

(19)



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(11)

**EP 0 669 317 B1**

(12)

**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
**04.09.2002 Bulletin 2002/36**

(51) Int Cl.7: **C07D 207/16**, C07D 211/60,  
C07D 403/06, C07D 403/12,  
C07D 401/12, C07D 403/08,  
C07D 403/10, C07K 5/06,  
A61K 31/40

(21) Application number: **95101059.4**

(22) Date of filing: **26.01.1995**

(54) **Prolineamide derivatives**

Prolineamid-Derivate

Dérivés de la prolinamide

(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL**  
**PT SE**  
Designated Extension States:  
**LT SI**

(30) Priority: **27.01.1994 JP 773394**

(43) Date of publication of application:  
**30.08.1995 Bulletin 1995/35**

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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## Description

## FIELD OF THE INVENTION

[0001] The present invention relates to novel proline derivatives. More particularly, it relates to proline derivatives having a protease inhibition activity or pharmaceutically acceptable salts thereof and protease inhibitors containing the same as an active ingredient.

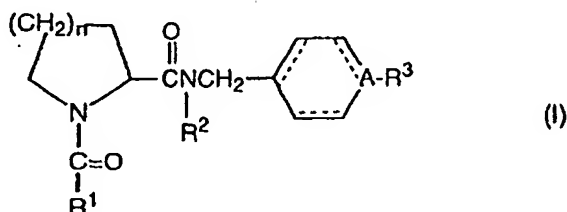
## BACKGROUND OF THE INVENTION

[0002] It has been known that various proteases are present in the living body, for example, a group of serine proteases such as thrombin, factor Xa, factor IXa, factor VIIa, trypsin, plasmin, tissue plasminogen activator, kallikrein, C3/C5 convertase in the complement system, tryptase, etc. is known. Further, it is also known that these proteases cause various diseases when they are activated abnormally by some reason. Accordingly, substances which inhibit the activity of these proteases are useful as a clinical remedy. For example, antithrombin agents, anti-factor Xa agents and anti-factor VIIa agents are useful for treating thrombosis, antitrypsin agents are useful for treating pancreatitis, antiplasmin agents are useful as hemostatics, antiallergic agents and antiinflammatory agents, antikallikrein agents are useful as a remedy for inflammation and ulcer, and anticomplementary agents are useful as a remedy for nephritis and rheumatoid arthritis. Protease inhibitors having these actions have hitherto been developed, but they are not necessarily sufficient for practical use in view of protease inhibition activity, stability in the living body and the like. For example, tripeptide derivatives consist of arginine derivatives are known as protease inhibitors. That is, D-phenylalanyl-L-prolyl-L-arginal is known as a thrombin inhibitor (e.g. Folia Haematol., 109, 22 (1982)) but is fairly unstable in the living body (J. Med. Chem., 33, 1729 (1990)). Further, arginal derivatives (Japanese Laid-open Patent Publication No. 4-89498) or amidinophenylalanine derivatives (Thromb. Res., 17, 425 (1980)) are reported as protease inhibitors but their inhibition activity is low.

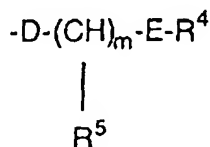
[0003] Under these circumstances, the present inventors have studied to develop structurally novel drugs having enzyme inhibition activity and stability in vivo, which are sufficient for practical use. As a result, it has been found that certain prolineamide derivatives can attain the desired object, thus the present invention has been established.

## SUMMARY OF THE INVENTION

[0004] That is, the present invention provides a prolineamide derivative represented by the formula (I):



wherein A is a carbon atom or a nitrogen atom; n is an integer of 0 to 2; a broken line is absent or a single bond; R¹ is



{wherein D and E independently indicate a single bond or an optionally branched C₁-C₆ alkylene group;

R⁴ is a C₁-C₆ alkyl group, -OR⁶ (R⁶ is a hydrogen atom, a C₁-C₆ alkyl group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group or an optionally substituted C₇-C₁₂ aralkyl group), -SR⁷ (R⁷ is a C₁-C₆ alkyl group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group

or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group), -SOR<sup>8</sup> (R<sup>8</sup> is an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group or an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group), -SO<sub>2</sub>R<sup>9</sup> (R<sup>9</sup> is an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group or an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group), -COR<sup>10</sup> (R<sup>10</sup> is a hydroxyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group or an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group), -NHR<sup>11</sup> (R<sup>11</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group), -NHCOR<sup>12</sup> (R<sup>12</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyloxy group), -NHSO<sub>2</sub>R<sup>13</sup> (R<sup>13</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group, an optionally substituted 5- to 10-membered heterocyclic group), an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, an optionally substituted 5- to 10-membered heterocyclic group or -SiR<sup>14</sup>R<sup>15</sup>R<sup>16</sup> (R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> independently indicate a C<sub>1</sub>-C<sub>6</sub> alkyl group);

R<sup>5</sup> is a -OR<sup>17</sup> (R<sup>17</sup> is a hydrogen atom, -SiR<sup>22</sup>R<sup>23</sup>R<sup>24</sup> (R<sup>22</sup>, R<sup>23</sup>, and R<sup>24</sup> independently indicate a C<sub>1</sub>-C<sub>6</sub> alkyl group), a C<sub>1</sub>-C<sub>6</sub> alkyl group or an optionally substituted 5- to 10-membered heterocyclic group), -OCOR<sup>18</sup> (R<sup>18</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, an amino group, a C<sub>1</sub>-C<sub>6</sub> alkylamino group, a C<sub>2</sub>-C<sub>12</sub> dialkylamino group or a C<sub>2</sub>-C<sub>7</sub> alkenylamino group), -NHR<sup>19</sup> (R<sup>19</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group), -NHCOR<sup>20</sup> (R<sup>20</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> haloalkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkenyloxy group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group, a C<sub>2</sub>-C<sub>12</sub> dialkylamino group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> haloalkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkyl group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group); and m is 0 or 1);

each of said 5- to 10-membered heterocyclic groups is independently selected from a furan ring, a tetrahydrofuran ring, a pyran ring, a benzofuran ring, a chroman ring, a thiophene ring, a benzothiophene ring, a pyrrole ring, an imidazole ring, a pyrazole ring, a triazole ring, a pyridine ring, a piperidine ring, a pyrazine ring, a piperazine ring, a pyrimidine ring, an indole ring, a benzimidazole ring, a purine ring, a quinoline ring, a phthalazine ring, a quinazoline ring, a cinnoline ring, an oxazole ring, a thiazole ring and a morpholine ring;

each of said optional substituents being independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> haloalkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyloxy group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>8</sub>-C<sub>13</sub> aralkyloxy carbonyl group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarboxyalkoxy group and a halogen atom);

R<sup>2</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group; and R<sup>3</sup> is -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> is a hydrogen atom or a hydroxyl group) or -NH<sub>2</sub>; provided that R<sup>3</sup> is -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> is as defined above) when A is a nitrogen atom, or a salt or hydrate thereof;

with the proviso that if the substituent R<sup>2</sup> represents a hydrogen atom, the group "D" represents a single bond, and the index n is 1 or 2, then neither of the substituents R<sup>4</sup> or R<sup>5</sup> represents a group including an aminosulfonyl moiety; and pharmaceutical use thereof.

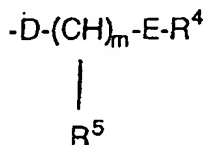
#### DETAILED DESCRIPTION OF THE INVENTION

**[0005]** The prolineamide derivative of the present invention is represented by the above formula (I). Examples of the optionally branched C<sub>1</sub>-C<sub>6</sub> alkylene group in the above definition include -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-, -(CH<sub>2</sub>)<sub>5</sub>-, -(CH<sub>2</sub>)<sub>6</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)- and the like. Examples of the C<sub>1</sub>-C<sub>6</sub> alkyl group include methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, s-butyl group, i-butyl group, t-butyl group, n-pentyl group, n-hexyl group and the like. Examples of the C<sub>1</sub>-C<sub>3</sub> alkyl group include those having three carbon atoms or less among those illustrated above. Examples of the C<sub>1</sub>-C<sub>6</sub> alkoxy group include methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butyloxy group, s-butyloxy group, i-butyloxy group, t-butyloxy group, n-pentyloxy group, n-hexyloxy group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group include methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, i-propoxycarbonyl group, n-butyloxycarbonyl group, t-butyloxycarbonyl group, n-pentyloxycarbonyl group, n-hexyloxycarbonyl group and the like. Examples of the C<sub>3</sub>-C<sub>8</sub> cycloalkyl group include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like. Examples of the C<sub>6</sub>-C<sub>10</sub> aryl group include phenyl group, tolyl group, naphthyl group and the like. Examples of the C<sub>7</sub>-C<sub>12</sub> aralkyl group include benzyl group, phenylethyl group, phenylpropyl group, naphthylmethyl group and the like. Examples of the C<sub>6</sub>-C<sub>10</sub> aryloxy group include phenyloxy group, naphthyloxy group and the like. Examples of the C<sub>7</sub>-C<sub>12</sub> aralkyloxy group include benzyloxy group, phenylethyloxy group, phenylpropyloxy group, naphthylmethyloxy group and the like. Examples of the C<sub>1</sub>-C<sub>6</sub> haloalkyl group include chloromethyl group, bromomethyl group, dichloromethyl group, 1-chloroethyl group, 2-chloroethyl group, 3-chloropropyl group, 4-chlorobutyl group, 5-chloropentyl group, 6-chlorohexyl group, difluoromethyl group, trifluoromethyl group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group include carboxymethyl group,

2-carboxyethyl group, 3-carboxypropyl group, 4-carboxybutyl group, 5-carboxypentyl group, 6-carboxyhexyl group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> carboxyalkyloxy group include carboxymethoxy group, 2-carboxyethoxy group, 3-carboxypropoxy group, 4-carboxybutyloxy group, 5-carboxypentyloxy group, 6-carboxyhexyloxy group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> alkenyloxy group include vinyloxy group, aryloxy group, 2-propenyloxy group, isopropenyloxy group, 3-butenyloxy group, 4-pentenyl group, 5-hexenyloxy group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> alkenylamino group include vinylamino group, arylamino group, 2-propenylamino group, isopropenylamino group, 3-butenylamino group, 4-pentenylamino group, 5-hexenylamino group and the like. Examples of the C<sub>1</sub>-C<sub>6</sub> alkylamino group include methylamino group, ethylamino group, n-propylamino group, n-butylamino group and the like. Examples of the C<sub>2</sub>-C<sub>12</sub> dialkylamino group include dimethylamino group, methylethylamino group, diethylamino group, di-n-propylamino group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> acyl group include acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group, hexanoyl group, heptanoyl group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> acyloxy group include acetyloxy group, propionyloxy group, butyryloxy group, isobutyryloxy group, valeryloxy group, isovaleryloxy group, pivaloyloxy group, hexanoyloxy group, heptanoyloxy group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group include methoxycarbonyloxy group, ethoxycarbonyloxy group, n-propoxycarbonyloxy group, n-butyloxycarbonyloxy group, n-pentyloxycarbonyloxy group, n-hexyloxycarbonyloxy group and the like. Examples of the C<sub>2</sub>-C<sub>7</sub> hydroxyalkylcarbonyloxy group include hydroxymethylcarbonyloxy group, 2-hydroxyethylcarbonyloxy group, 3-hydroxypropylcarbonyloxy group, 4-hydroxybutylcarbonyloxy group, 5-hydroxypentylcarbonyloxy group, 6-hydroxyhexylcarbonyloxy group and the like. Examples of the C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group include methoxycarbonylmethoxy group, ethoxycarbonylmethoxy group, propoxycarbonylmethoxy group, methoxycarbonylethoxy group, ethoxycarbonylethoxy group, propoxycarbonylethoxy group and the like. Examples of the C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkyl group include methoxycarbonylmethyl group, ethoxycarbonylmethyl group, propoxycarbonylmethyl group, methoxycarbonylethyl group, ethoxycarbonylethyl group, propoxycarbonylethyl group and the like. Examples of the above "optional substituents" include those given above for the respective group of compounds. Examples of the C<sub>8</sub>-C<sub>13</sub> aralkyloxycarbonyl group include benzyloxycarbonyl group, phenylethylloxycarbonyl group, phenylpropylloxycarbonyl group, naphthylmethylloxycarbonyl group, etc. Examples of the halogen atom include fluorine atom, chlorine atom, bromine atom and the like.

[0006] In the compound represented by the above formula (I) of the present invention, a carbon atom is preferred as A.

[0007] Examples of preferred compounds of the present invention include those of the formula (I), wherein A is a carbon atom; n is 1 or 2; R<sup>1</sup> is



(wherein D and E independently indicate a single bond or an optionally branched C<sub>1</sub>-C<sub>6</sub> alkylene group;

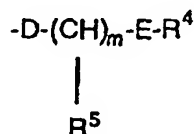
R<sup>4</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group: -OR<sup>6</sup> (R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C<sub>7</sub>-C<sub>12</sub> aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -SR<sup>7</sup> (R<sup>7</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); or a C<sub>7</sub>-C<sub>12</sub> aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -COOH: a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; a C<sub>3</sub>-C<sub>8</sub> cycloalkyl group;

or -SiR<sup>14</sup>R<sup>15</sup>R<sup>16</sup> (R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> independently indicate a C<sub>1</sub>-C<sub>6</sub> alkyl group);

R<sup>5</sup> is -OH, -OCOR<sup>18</sup> (R<sup>18</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group or a C<sub>2</sub>-C<sub>7</sub> alkenylamino group), -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a C<sub>6</sub>-C<sub>10</sub> aryloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group, a C<sub>2</sub>-C<sub>12</sub> dialkylamino group or a C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>6</sub>-C<sub>10</sub> aryl group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkyl group or a C<sub>7</sub>-C<sub>12</sub> aralkyl group); and m is 0 or 1; and

R<sup>2</sup> is a hydrogen atom.

**[0008]** As the more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R<sup>1</sup> is



{wherein D and E independently indicate a single bond or an optionally branched C<sub>1</sub>-C<sub>6</sub> alkylene group;

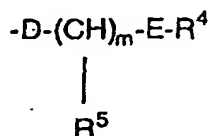
R<sup>4</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; -OR<sup>6</sup> (R<sup>6</sup> is a C<sub>6</sub>-C<sub>10</sub> aryl or C<sub>7</sub>-C<sub>12</sub> aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group); -SR<sup>7</sup> (R<sup>7</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group); a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group; or a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group;

R<sup>5</sup> is -OH, -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group or a C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group or a C<sub>6</sub>-C<sub>10</sub> aryl group);

and m is 1; and

R<sup>2</sup> is a hydrogen atom.

**[0009]** As the more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R<sup>1</sup> is



{wherein D is a single bond and E is a single bond or a C<sub>1</sub>-C<sub>6</sub> alkylene group;

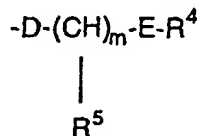
R<sup>4</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; -OR<sup>6</sup> (R<sup>6</sup> is a C<sub>6</sub>-C<sub>10</sub> aryl or C<sub>7</sub>-C<sub>12</sub> aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group); -SR<sup>7</sup> (R<sup>7</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group); a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group; or a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group;

R<sup>5</sup> is -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group or a C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group or a C<sub>6</sub>-C<sub>10</sub> aryl group);

and m is 1; and

R<sup>2</sup> is a hydrogen atom.

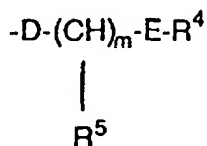
**[0010]** As the still more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R<sup>1</sup> is



(wherein D is a single bond; E is a single bond or a C<sub>1</sub>-C<sub>3</sub> alkylene group; R<sup>4</sup> is a C<sub>3</sub>-C<sub>6</sub> alkyl group, -OR<sup>6</sup> (R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group), a phenyl group or a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group; R<sup>5</sup> is -OH, -NHR<sup>19</sup> (R<sup>19</sup> is a hydrogen atom), -NHCOR<sup>20</sup>

(R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>3</sub> alkyl group); and m is 1); and R<sup>2</sup> is a hydrogen atom.

**[0011]** As the particularly preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R<sup>1</sup> is



{wherein D is a single bond; E is a single bond or a C<sub>1</sub>-C<sub>6</sub> alkylene group; R<sup>4</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; R<sup>5</sup> is -NHCOR<sup>20</sup> (R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group); and m is 1};

R<sup>2</sup> is a hydrogen atom; and

R<sup>3</sup> is -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> is a hydrogen atom or a hydroxyl group)).

**[0012]** As the most preferred compound of the present invention, there is trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 461 in Table 1 in Example 33).

**[0013]** The prolineamide derivatives represented by the above formula (I) can afford various stereoisomers. For example, concerning asymmetric carbon atoms, the absolute configuration may be D-configuration, L-configuration or DL configuration and all types thereof are included in the compounds of the present invention.

**[0014]** Examples of the salt which can be formed with the compounds of the above formula (I) of the present invention include inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.; organic acid salts such as succinate, oxalate, fumarate, maleate, lactate, tartrate, citrate, acetate, glycolate, methanesulfonate, toluenesulfonate, etc. Further, the proline derivatives of the above formula (I) containing a free carboxyl group can also form a salt with a pharmaceutically acceptable base.

**[0015]** Examples of the salt include alkaline metal salt, alkaline earth metal salt, ammonium salt, alkyl ammonium salt and the like.

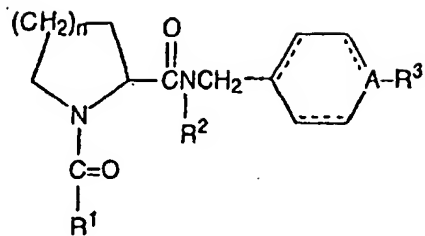
**[0016]** Further, the prolineamide derivatives of the above formula (I) and the salts thereof can also form a hydrate.

**[0017]** Hereinafter, examples of the compounds of the present invention will be described.

**[0018]** The following compounds were deleted during prosecution;

77-81, 104, 106-110, 112-163, 165-172, 230-233, 237, 239, 241, 243, 245-246, 250-253, 269-270, 274, 276, 283-284, 291-293, 295, 302-305, 317, 319, 321, 324, 326, 328, 382, 398-399, 437-442, 452, 501-504, 510, 515-746, 751, 759-760, 772-775, 788-792, 805-815, 820, 828-829, 834, 898-971, 973-976, 996-1002, 1004-1006. Compounds No. 105 and 776 were designated as Reference compounds.

Table 1



Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
1		-H		1	C	Single bond
2		-H		1	C	Single bond
3		-H		1	C	Single bond
4		-H		1	C	Single bond
5		-H		1	C	Single bond
6		-H		1	C	Single bond
7		-H		1	C	Single bond
8		-H		1	C	Single bond

Table 1 (continued)

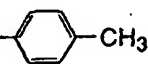
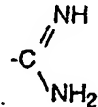
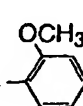
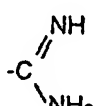
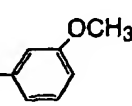
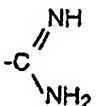
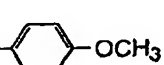
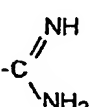

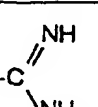

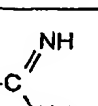
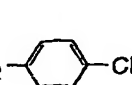
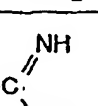
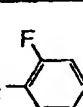
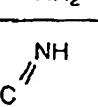
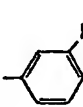
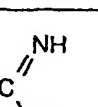
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9	$-(CH_2)_2$ - 	-H		1	C	Single bond
10	$-(CH_2)_2$ - 	-H		1	C	Single bond
11	$-(CH_2)_2$ - 	-H		1	C	Single bond
12	$-(CH_2)_2$ - 	-H		1	C	Single bond
13	$-(CH_2)_2$ - 	-H		1	C	Single bond
14	$-(CH_2)_2$ - 	-H		1	C	Single bond
15	$-(CH_2)_2$ - 	-H		1	C	Single bond
16	$-(CH_2)_2$ - 	-H		1	C	Single bond
17	$-(CH_2)_2$ - 	-H		1	C	Single bond



Table 1 (continued)

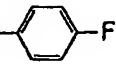
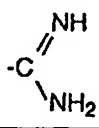
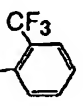
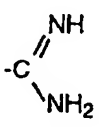

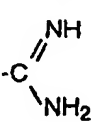
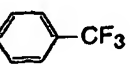
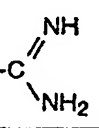

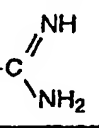

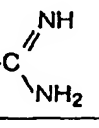
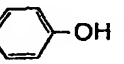
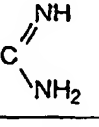

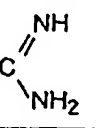
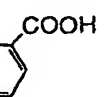
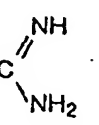
Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
18	$-(CH_2)_2$ - 	-H		1	C	Single bond
19	$-(CH_2)_2$ - 	-H		1	C	Single bond
20	$-(CH_2)_2$ - 	-H		1	C	Single bond
21	$-(CH_2)_2$ - 	-H		1	C	Single bond
22	$-(CH_2)_2$ - 	-H		1	C	Single bond
23	$-(CH_2)_2$ - 	-H		1	C	Single bond
24	$-(CH_2)_2$ - 	-H		1	C	Single bond
25	$-(CH_2)_2$ - 	-H		1	C	Single bond
26	$-(CH_2)_2$ - 	-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
27	$-(CH_2)_2-\text{C}_6\text{H}_4-\text{COOH}$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
28	$-(CH_2)_2-\text{C}_6\text{H}_4-\text{CH}_2\text{COOH}$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
29	$-(CH_2)_2-\text{C}_6\text{H}_4-\text{OCH}_2\text{COOH}$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
30	$-(CH_2)_2-\text{C}_6\text{H}_4-\text{COOCH}_3$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
31	$-(CH_2)_2-\text{C}_6\text{H}_4-\text{COOCH}_2-\text{C}_6\text{H}_5$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
32	$-(CH_2)_2-\text{C}_6\text{H}_4-\text{COCH}_3$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
33	$-\text{CH}_2-\text{C}_5\text{H}_9$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
34	$-(CH_2)_2-\text{C}_6\text{H}_{11}$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
35	$-(CH_2)_2-\text{C}_6\text{H}_7(\text{CH}_3)_2$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond
36	$-(CH_2)_2-\text{C}_4\text{H}_3\text{S}$	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	1	C	Single bond

Table 1 (continued)


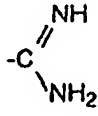

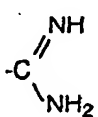

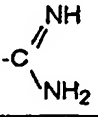
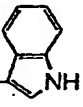
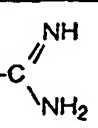
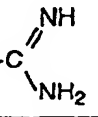
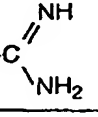
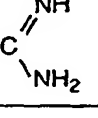
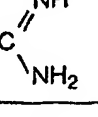
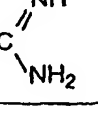

Compound No.	$-R^1 \left( \begin{array}{c} \cdot D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
37	$-(CH_2)_2$ 	-H		1	C	Single bond
38	$-(CH_2)_2$ 	-H		1	C	Single bond
39	$-(CH_2)_2$ -N  -CH <sub>3</sub>	-H		1	C	Single bond
40	$-(CH_2)_2$ 	-H		1	C	Single bond
41	-CH <sub>3</sub>	-H		1	C	Single bond
42	-CH <sub>2</sub> CH <sub>3</sub>	-H		1	C	Single bond
43	$-(CH_2)_2$ CH <sub>3</sub>	-H		1	C	Single bond
44	-CH(CH <sub>3</sub> ) <sub>2</sub>	-H		1	C	Single bond
45	$-(CH_2)_3$ CH <sub>3</sub>	-H		1	C	Single bond
46	-C(CH <sub>3</sub> ) <sub>3</sub>	-H		1	C	Single bond

Table 1 (continued)

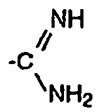
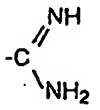
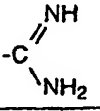
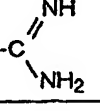
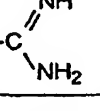
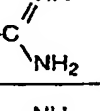

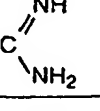

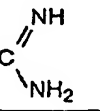

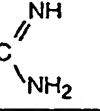
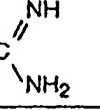
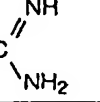
Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
47	$-(CH_2)_4CH_3$	-H		1	C	Single bond
48	$-CH_2CH_2C(CH_3)_3$	-H		1	C	Single bond
49	$-(CH_2)_9CH_3$	-H		1	C	Single bond
50	$-CH_2Si(CH_3)_3$	-H		1	C	Single bond
51	$-CH_2CH_2Si(CH_3)_3$	-H		1	C	Single bond
52	$-CH_2OCH_3$	-H		1	C	Single bond
53	$-CH_2O$ 	-H		1	C	Single bond
54	$-CH_2O$ 	-H		1	C	Single bond
55	$-CH_2OCH_2$ 	-H		1	C	Single bond
56	$-CH_2OH$	-H		1	C	Single bond
57	$-CH_2SCH_3$	-H		1	C	Single bond

Table 1 (continued)


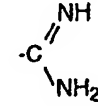

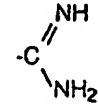

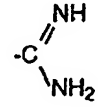

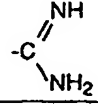

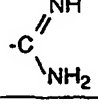

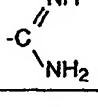

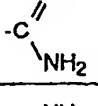

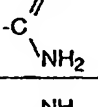

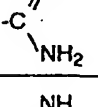
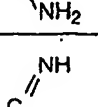

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
58	$-\text{CH}_2\text{S}-$ 	-H		1	C	Single bond
59	$-\text{CH}_2\text{S}-$ 	-H		1	C	Single bond
60	$-\text{CH}_2\text{SCH}_2-$ 	-H		1	C	Single bond
61	$-\text{CH}_2\text{SO}-$ 	-H		1	C	Single bond
62	$-\text{CH}_2\text{SO}-$ 	-H		1	C	Single bond
63	$-\text{CH}_2\text{SO}_2-$ 	-H		1	C	Single bond
64	$-\text{CH}_2\text{SO}_2-$ 	-H		1	C	Single bond
65	$-\text{CH}_2\text{CO}-$ 	-H		1	C	Single bond
66	$-\text{CH}_2\text{CO}-$ 	-H		1	C	Single bond
67	$-\text{CH}_2\text{COOH}$	-H		1	C	Single bond
68	$-\text{CH}_2\text{COOCH}_3$	-H		1	C	Single bond

Table 1 (continued)







Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
69	$-CH_2NHCH_3$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
70	$-CH_2NH-$ 	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
71	$-CH_2NH-$ 	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
72	$-CH_2NHCH_2-$ 	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
73	$-CH_2NHCOOCH_3$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
74	$-CH_2NHCO-$ 	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
75	$-CH_2NHCO-$ 	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
76	$-CH_2NHCOOCH_2-$ 	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

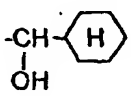
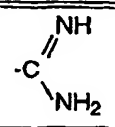
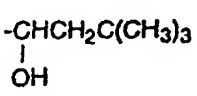
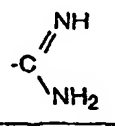
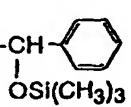
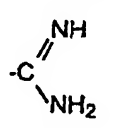
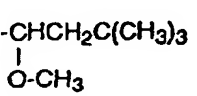
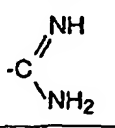
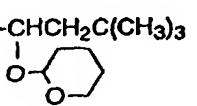
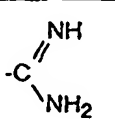
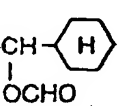
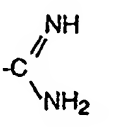
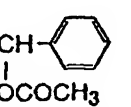
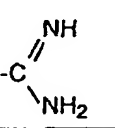
Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
82		-H		1	C	Single bond
83		-H		1	C	Single bond
84		-H		1	C	Single bond
85		-H		1	C	Single bond
86		-H		1	C	Single bond
87		-H		1	C	Single bond
88		-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
89	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OCOOCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
90	$\begin{array}{c} -CH-\text{Cyclohexyl} \\   \\ OCONH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
91	$\begin{array}{c} -CH-\text{Phenyl} \\   \\ OCONHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
92	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OCON(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
93	$\begin{array}{c} -CH_2CH-\text{Cyclohexyl} \\   \\ OCONHCH_2CH=CH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
94	$\begin{array}{c} -CHCH_2-\text{Phenyl} \\   \\ NHCHO \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
95	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
96	$\begin{array}{c} -CHCH_2-\text{Cyclohexyl} \\   \\ NHCOCF_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
97	$\begin{array}{c} -CHCH_2-\text{Phenyl} \\   \\ NHCOOCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond



Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
98	$\begin{array}{c} -CHC(SCH_3)(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
99	$\begin{array}{c} -CH-\text{C}_6\text{H}_{11} \\   \\ NHCO-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
100	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NHCO-\text{C}_6\text{H}_{11} \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
101	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
102	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ NHCOOCH_2CH=CH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
103	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{COOH} \\   \\ NHCOOCH_2\text{COOH} \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
105 (Reference)	$\begin{array}{c} -CH-\text{C}_6\text{H}_{11} \\   \\ NH\text{SO}_2\text{CH}_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
111	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NH\text{SO}_2\text{CH}_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
164	$\begin{array}{c} -CH_2CH(CH_2)_3CH_3 \\   \\ NHSO_2CF_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
173	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
174	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
175	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{COOCH}_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
176	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{CH}_2\text{COOH} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
177	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{COCH}_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
178	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{COOH} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
179	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
180	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
181	$\begin{array}{c} -CHCH_2O-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
182	$\begin{array}{c} -CHCH_2O-\text{C}_6\text{H}_4-OH \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
183	$\begin{array}{c} -CHCH_2O-\text{C}_6\text{H}_{11} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
184	$\begin{array}{c} -CHCH_2S-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
185	$\begin{array}{c} -CHCH_2S-\text{C}_6\text{H}_4-Cl \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
186	$\begin{array}{c} -CHCH_2S-\text{C}_6\text{H}_{11} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
187	$\begin{array}{c} -CH-\text{C}_6\text{H}_{11} \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
188	$\begin{array}{c} -CHCH_2-\text{Cyclohexyl} \\   \\ NHC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
189	$\begin{array}{c} -CHCH_2-\text{Phenyl} \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
190	$\begin{array}{c} -CHCH_2-\text{Cyclohexyl}-OCH_2COOH \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
191	$\begin{array}{c} -CHCH_2-\text{Cyclohexyl}-COOH \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
192	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
193	$\begin{array}{c} -CHCH_2O-\text{Cyclohexyl} \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
194	$\begin{array}{c} -CHCH_2S-\text{Cyclohexyl} \\   \\ NHCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
195	$\begin{array}{c} -CHCH_2-\text{Cyclohexyl} \\   \\ NHCH_2-\text{Phenyl} \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
196		-H		1	C	Single bond
197		-H		1	C	Single bond
198		-H		1	C	Single bond
199		-H		1	C	Single bond
200		-H		1	C	Single bond
201		-H		1	C	—
202		-H		1	C	—
203		-H		1	C	—
204	$-(CH_2)_2CH_3$	-H		1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	-R2	-R3	n	A	Broken line
205		-H		1	C	—
206		-H		1	C	—
207		-H		1	C	—
208		-H		1	C	—
209		-H		1	C	—
210		-H		1	C	—
211		-H		1	C	—
212		-H		1	C	—
213		-H		1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
214		-H		1	C	—
215		-H		1	C	—
216		-H		1	C	—
217		-H		1	C	—
218		-H		1	C	—
219		-H		1	C	—
220		-H		1	C	—
221		-H		1	C	—
222		-H		1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
223	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOC_2H_5 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—
224	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOCH_3 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—
225	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCHO \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—
226	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH_3 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—
227	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—
228	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—
229	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\ \backslash \\ \text{NH}_2 \end{array}$	1	C	—



Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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234	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ \text{NH}_2 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	1	C	—
235	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{OH} \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	1	C	—
236	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{OH} \\   \\ \text{OH} \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	1	C	—

238	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	1	C	—
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Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5- \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
240	$\begin{array}{c} -CHCH_2OC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
242	$\begin{array}{c} -CHCH(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
244	$\begin{array}{c} -CHC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
247	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
248	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
249	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-COOH \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

254	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NHCHO \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
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Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
255	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-F \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
256	$\begin{array}{c} CH_3 \\   \\ -CHCH_2-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
257	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
258	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
259	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ OCOCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
260	$\begin{array}{c} -CHC(SCH_3)(CH_3)_2 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
261	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OCONHCH_2CH=CH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
262	$\begin{array}{c} -CH(CH_2)_3CH_3 \\   \\ NHCOOCH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
263	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
264	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
265	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
266	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
267	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
268	$\begin{array}{c} -CH_2CH(CH_2)_2CH_3 \\   \\ NHSO_2CH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
271	$\begin{array}{c} -CH_2CH(CH_2)_2CH_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
272	$-(CH_2)_2-\text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	N	—
273	$-CH_2OCH_2-\text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	N	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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275	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCHO \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
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277	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
278	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
279	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
280	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
281	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCONHCH_2CH=CH_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
282	$\begin{array}{c} -CH- \\   \\ OH \end{array} \text{---} \text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C- \\ \backslash \\ NH_2 \end{array}$	1	N	—

285	$\begin{array}{c} -CHCH_2- \\   \\ NHCOOC_2H_5 \end{array} \text{---} \text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C- \\ \backslash \\ NH_2 \end{array}$	1	N	—
286	$\begin{array}{c} -CH- \\   \\ NHCOOCH(CH_3)_2 \end{array} \text{---} \text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C- \\ \backslash \\ NH_2 \end{array}$	1	N	—
287	$\begin{array}{c} -CH- \\   \\ NHCOOC(CH_3)_3 \end{array} \text{---} \text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C- \\ \backslash \\ NH_2 \end{array}$	1	N	—
288	$\begin{array}{c} -CHCH_2- \\   \\ NHCOOC(CH_3)_3 \end{array} \text{---} \text{C}_6\text{H}_5$	-H	$\begin{array}{c} NH \\ // \\ -C- \\ \backslash \\ NH_2 \end{array}$	1	N	—
289	$\begin{array}{c} -CH- \\   \\ NHCOOCH(CH_3)_2 \end{array} \text{---} \text{C}_5\text{H}_9$	-H	$\begin{array}{c} NH \\ // \\ -C- \\ \backslash \\ NH_2 \end{array}$	1	N	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
290	$\begin{array}{c} -CH- \text{Hexagon} \\   \\ OH \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—

294	$\begin{array}{c} -CHC(SCH_3)(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
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296	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
297	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
298	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
299	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—



Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
300	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
301	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—

306	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond
307	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond
308	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond

Table 1 (continued)







Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
309	$-(CH_2)_3-$ 	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
310	$-\text{CHCH}_2-$    NH <sub>2</sub>	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
311	$-\text{CH}-$    NHCOOCH(CH <sub>3</sub> ) <sub>2</sub>	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
312	$-\text{CHCH}_2\text{C}(\text{C}_2\text{H}_5)_2$   NHCOOC(CH <sub>3</sub> ) <sub>3</sub>	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
313	$-\text{CHCH}_2\text{C}(\text{CH}_3)_3$   OH	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
314	$-\text{CH}_2\text{CH}-$    NHSO <sub>2</sub> CH <sub>3</sub>	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
315	$-\text{CHCH}_2-$    OCOOC <sub>2</sub> H <sub>5</sub>	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond
316	$-\text{CH}-$    OH	-H	$\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{NH}_2 \end{array}$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
318	$\begin{array}{c} -CH- \text{C}_6\text{H}_{11} \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
320	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
322	$\begin{array}{c} -CHCH_2CH(\text{C}_2\text{H}_5)_2 \\   \\ \text{NHCOOC}(\text{CH}_3)_3 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
323	$\begin{array}{c} -CHCH_2C(\text{CH}_3)_3 \\   \\ \text{OH} \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
325	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ \text{NHCOOC}(\text{CH}_3)_3 \end{array}$	-H	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	N	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
327	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—

329	$\begin{array}{c} -CH(CH_2)_2SCH_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
330	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
331	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	-CH <sub>3</sub>	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
332	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-CH <sub>3</sub>	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
333	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	-CH <sub>3</sub>	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
334	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-CH <sub>3</sub>	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
335	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	-CH <sub>3</sub>	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
336	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
337	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
338	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
339	$\begin{array}{c} -CH-\text{C}_6\text{H}_{11} \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
340	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
341	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
342	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
343	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
344	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
345	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
346	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
347	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
348	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{OCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
349	$\begin{array}{c} -CHCH_2\text{C}(\text{CH}_3)_3 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
350	$\begin{array}{c} -CHCH_2\text{CH}(\text{C}_2\text{H}_5)_2 \\   \\ \text{NHCOOC}(\text{CH}_3)_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
351	$\begin{array}{c} -CHCH_2\text{C}(\text{CH}_3)_3 \\   \\ \text{OH} \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	1	N	—
352	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	2	C	Single bond
353	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -\text{C} \\ \backslash \\ \text{NH}_2 \end{array}$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
354	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	Single bond
355	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ \text{OCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	Single bond
356	$\begin{array}{c} -CHCH_2\text{C}(\text{CH}_3)_3 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	Single bond
357	$\begin{array}{c} -CH(\text{CH}_2)_4\text{CH}_3 \\   \\ \text{NHCOOC}(\text{CH}_3)_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	Single bond
358	$\begin{array}{c} -CHCH_2CH(\text{CH}_3)_2 \\   \\ \text{OH} \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	Single bond
359	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
360	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
361	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—
362	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ \text{OCOOC}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$\begin{array}{c} \text{NH} \\ // \\ -C \\   \\ \text{NH}_2 \end{array}$	2	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
363	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	—
364	$\begin{array}{c} -CHC(SCH_3)(CH_3)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	—
365	$\begin{array}{c} -CHCH_2CH(CH_3)_3 \\   \\ NH_2 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	—
366	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
367	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
368	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
369	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4-\text{COOH} \\   \\ OCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
370	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHSO_2CH_2COOH \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
371	$\begin{array}{c} -CH(CH_2)_2SCH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—
372	$\begin{array}{c} -CH_2CH(CH_2)_3CH_3 \\   \\ OH \end{array}$	$-CH_3$	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	N	—



Table 1 (continued)


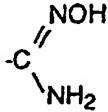
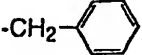
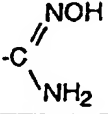
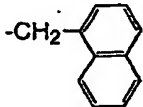
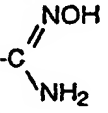
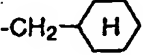
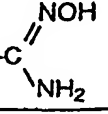
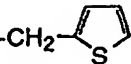
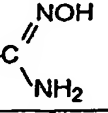
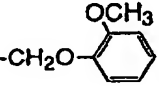
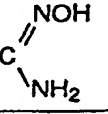
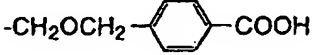
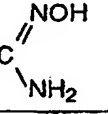
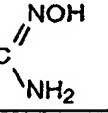
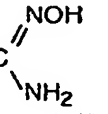
Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
373		-H		1	C	Single bond
374		-H		1	C	Single bond
375		-H		1	C	Single bond
376		-H		1	C	Single bond
377		-H		1	C	Single bond
378		-H		1	C	Single bond
379		-H		1	C	Single bond
380	$-CH_2SC_2H_5$	-H		1	C	Single bond
381	$-(CH_2)_4COOH$	-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
383	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
384	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
385	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
386	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NHCHO \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
387	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
388	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
389	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
390	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
391		-H		1	C	Single bond
392		-H		1	C	Single bond
393		-H		1	C	Single bond
394		-H		1	C	Single bond
395		-H		1	C	Single bond
396		-H		1	C	Single bond
397		-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
400	$\begin{array}{c} -CHCH_2- \\   \\ NH_2 \end{array} \text{---} \text{Cyclohexyl}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
401	$\begin{array}{c} -CH- \\   \\ OH \end{array} \text{---} \text{Cyclohexyl}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
402	$\begin{array}{c} -CH- \\   \\ NH_2 \end{array} \text{---} \text{Cyclohexyl}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
403	$\begin{array}{c} -CH- \\   \\ NHCOOC_2H_5 \end{array} \text{---} \text{Cyclohexyl}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
404	$\begin{array}{c} -CH- \\   \\ NHCOOC(CH_3)_3 \end{array} \text{---} \text{Cyclohexyl}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
405	$\begin{array}{c} -CHCH_2CH(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
406	$\begin{array}{c} -CHCH_2CH(CH_3)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
407	$\begin{array}{c} -CHCH(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
408	$\begin{array}{c} -CHCH(CH_3)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
409	$\begin{array}{c} -CHC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
410	$\begin{array}{c} -CHC(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
411	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
412	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
413	$\begin{array}{c} -CHCH_2CH_2SCH_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
414	$\begin{array}{c} -CHCH_2CH_2SCH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
415	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
416	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
417	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
418	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
419	$\begin{array}{c} -CHC(SCH_3)(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
420	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
421	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
422	$\begin{array}{c} -CH- \text{Cyclohexyl} \\   \\ OH \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
423	$\begin{array}{c} -CHCH_2- \text{Cyclohexyl} \\   \\ OCOCH_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
424	$\begin{array}{c} -CHCH_2- \text{Cyclohexyl} \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
425	$\begin{array}{c} -CH- \text{Cyclopentyl} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
426	$\begin{array}{c} -CHCH_2- \text{Cyclohexyl} \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
427	$\begin{array}{c} -CH- \text{Cyclohexyl} \\   \\ NHCHO \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
428	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
429	$\begin{array}{c} -CH-\text{C}_5\text{H}_9 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
430	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
431	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
432	$\begin{array}{c} -CH-\text{C}_5\text{H}_9 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
433	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
434	$\begin{array}{c} -CHCH_2-\text{C}_5\text{H}_9 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
435	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
436	$\begin{array}{c} -CH- \text{Cyclohexyl} \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

443	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
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Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
444	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
445	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ OCOCH_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
446	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
447	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
448	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
449	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
450	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
451	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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453	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ OH \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
454	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
455	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ OCOCH_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
456	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
457	$\begin{array}{c} -CH_2CH(CH_2)_2CH_3 \\   \\ NHCHO \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
458	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
459	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
460	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
461	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
462	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
463	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
464	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
465	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
466	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
467	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
468	$\begin{array}{c} -CH(CH_2)_2SCH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
469	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
470	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
471	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)


Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
472	$\begin{array}{c} -CH- \\   \\ NHCOOC(CH_3)_3 \end{array}$ 	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
473	$\begin{array}{c} -CHCH_2CH(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
474	$\begin{array}{c} -CHCH_2CH(CH_3)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
475	$\begin{array}{c} -CH(CH_2)_2CH_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
476	$\begin{array}{c} -CH(CH_2)_2CH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
477	$\begin{array}{c} -CHCH(CH_3)_2 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
478	$\begin{array}{c} -CHCH(CH_3)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
479	$\begin{array}{c} -CHC(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
480	$\begin{array}{c} -CHC(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
481	$\begin{array}{c} -CHCH_2Si(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
482	$\begin{array}{c} -CHCH_2Si(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
483	$\begin{array}{c} -CHCH_2CH_2SCH_3 \\   \\ NHCOOC_2H_5 \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
484	$\begin{array}{c} -CHCH_2CH_2SCH_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
485	$\begin{array}{c} -CHCH_2OC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
486	$\begin{array}{c} -CHCH_2OC(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
487	$\begin{array}{c} -CHCH_2OC(CH_3)_2C_2H_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
488	$\begin{array}{c} -CHCH_2OC(CH_3)_2C_2H_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
489	$\begin{array}{c} -CHCH_2OC(C_2H_5)_2CH_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
490	$\begin{array}{c} -CHCH_2OC(C_2H_5)_2CH_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
491	$\begin{array}{c} -CHCH_2OC(CH_3)_2CH(CH_3)_2 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
492	$\begin{array}{c} -CHCH_2SC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
493	$\begin{array}{c} -CHCH_2SC(CH_3)_2C_2H_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
494	$\begin{array}{c} -CHCH_2SC(CH_3)_2C_2H_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
495	$\begin{array}{c} -CHC(CH_3)_2SC_2H_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
496	$\begin{array}{c} -CHC(CH_3)_2SC_2H_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
497	$\begin{array}{c} -CHC(CH_3)_2SCH(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
498	$\begin{array}{c} -CHC(CH_3)_2SCH(CH_3)_2 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
499	$\begin{array}{c} -CHC(CH_3)_2SCH(C_2H_5)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
500	$\begin{array}{c} -CHC(CH_3)_2SCH(C_2H_5)_2 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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505	$\begin{array}{c} -CH-\text{H} \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
506	$\begin{array}{c} -CHCH_2-\text{H} \\   \\ NHCOOC_2H_5 \end{array}$	H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
507	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ NH_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
508	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—
509	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	N	—

511	$\begin{array}{c} -CHCH_2-\text{H} \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-CH <sub>3</sub>	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond
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Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
512	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond
513	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond
514	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$\begin{array}{c} NOH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	2	C	Single bond



Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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747	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	Single bond
748	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	Single bond
749	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	Single bond
750	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	1	C	Single bond

752	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	Single bond
753	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
754	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	Single bond
755	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	Single bond
756	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	1	C	Single bond
757	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	Single bond
758	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	Single bond

761	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
762	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
763	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	—
764	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
765	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
766	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	—
767	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
768	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	1	C	—
769	$-CH_2-\text{C}_6\text{H}_5$	-H	$-NH_2$	1	C	—
770	$-(CH_2)_3-\text{C}_6\text{H}_5$	-H	$-NH_2$	1	C	—
771	$-CH_2OCH_2-\text{C}_6\text{H}_5$	-H	$-NH_2$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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776 (Reference)	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	-H	$-\text{NH}_2$	1	C	—
777	$\begin{array}{c} -CH_2CH-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	-H	$-\text{NH}_2$	1	C	—
778	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCHO} \end{array}$	-H	$-\text{NH}_2$	1	C	—
779	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NH}_2 \end{array}$	-H	$-\text{NH}_2$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
780	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
781	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	—
782	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
783	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	1	C	—
784	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
785	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
786	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCONHCH_3 \end{array}$	-H	$-NH_2$	1	C	—
787	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCONHCH_2CH=CH_2 \end{array}$	-H	$-NH_2$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
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793	$\begin{array}{c} -CHC(SCH_3)(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
794	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
795	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
796	$\begin{array}{c} -CH(CH_2)_4CH_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
797	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	—
798	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \begin{pmatrix} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{pmatrix}$	$-R^2$	$-R^3$	$n$	A	Broken line
799	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
800	$\begin{array}{c} -CHCH_2CH(C_2H_5)_2 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
801	$\begin{array}{c} -CH(CH_2)_2SCH_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	1	C	—
802	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$-NH_2$	1	C	—
803	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OH \end{array}$	-H	$-NH_2$	1	C	—
804	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ OCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—

816	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	Single bond
817	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
818	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	2	C	Single bond
819	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	2	C	Single bond
821	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	Single bond
822	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	2	C	Single bond
823	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	2	C	Single bond
824	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	Single bond
825	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	2	C	Single bond
826	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	Single bond



Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
827	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	2	C	Single bond

830	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	—
831	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	2	C	—
832	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	2	C	—
833	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	2	C	—

835	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	—
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Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
836	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	2	C	—
837	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$-NH_2$	2	C	—
838	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	—
839	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	-H	$-NH_2$	2	C	—
840	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	2	C	—
841	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$-NH_2$	2	C	—
842	$\begin{array}{c} -CH-\text{C}_6\text{H}_4\text{H} \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
843	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4\text{H} \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
844	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_4\text{H} \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
845	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
846	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
847	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
848	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
849	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
850	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
851	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
852	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
853	$\begin{array}{c} -CH- \text{C}_6\text{H}_5 \\   \\ OH \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
854	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
855	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	1	C	Single bond
856	$\begin{array}{c} -CH- \text{C}_6\text{H}_{11} \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	—
857	$\begin{array}{c} -CHCH_2- \text{C}_6\text{H}_{11} \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	—
858	$\begin{array}{c} -CHCH_2- \text{C}_6\text{H}_{11} \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	1	C	—
859	$\begin{array}{c} -CHCH_2- \text{C}_6\text{H}_{11} \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	1	C	—
860	$\begin{array}{c} -CHCH_2- \text{C}_6\text{H}_{11} \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$-NH_2$	1	C	—
861	$\begin{array}{c} -CH- \text{C}_6\text{H}_{11} \\   \\ OH \end{array}$	$-CH_3$	$-NH_2$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
862	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
863	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
864	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
865	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}(\text{CH}_3)_3 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
866	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{OCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
867	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{OH} \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
868	$\begin{array}{c} -CHCH_2\text{C}(\text{CH}_3)_3 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
869	$\begin{array}{c} -CHCH_2\text{C}(\text{CH}_3)_3 \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	1	C	—
870	$\begin{array}{c} -CH-\text{C}_6\text{H}_4\text{H} \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
871	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
872	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
873	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
874	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}(\text{CH}_3)_3 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
875	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ \text{OH} \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
876	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHSO}_2\text{CH}_3 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
877	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOC}_2\text{H}_5 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond
878	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ \text{NHCOOCH}(\text{CH}_3)_2 \end{array}$	$-\text{CH}_3$	$-\text{NH}_2$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
879	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$-NH_2$	2	C	Single bond
880	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	2	C	Single bond
881	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	$-CH_3$	$-NH_2$	2	C	Single bond
882	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	2	C	Single bond
883	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	2	C	Single bond
884	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
885	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
886	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
887	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	2	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
888	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_{11} \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
889	$\begin{array}{c} -CH-\text{C}_6\text{H}_{11} \\   \\ OH \end{array}$	$-CH_3$	$-NH_2$	2	C	—
890	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHSO_2CH_3 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
891	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
892	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
893	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC(CH_3)_3 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
894	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ OCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
895	$\begin{array}{c} -CH-\text{C}_6\text{H}_5 \\   \\ OH \end{array}$	$-CH_3$	$-NH_2$	2	C	—
896	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	$-CH_3$	$-NH_2$	2	C	—
897	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	$-CH_3$	$-NH_2$	2	C	—



Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
972	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	Single bond
977	$\begin{array}{c} -CHCH_2OC(CH_3)_2C_2H_5 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
978	$\begin{array}{c} -CHCH_2OC(CH_3)_2C_2H_5 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—
979	$\begin{array}{c} -CHCH_2OC(C_2H_5)_2CH_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\ \backslash \\ NH_2 \end{array}$	1	C	—

Table 1 (continued)

Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
980	$\begin{array}{c} -CHCH_2SC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
981	$\begin{array}{c} -CHCH_2O \begin{array}{c} CH_3 \\   \\ \text{Cyclopentyl} \end{array} \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
982	$\begin{array}{c} -CHCH(CH_3)OC(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
983	$\begin{array}{c} -CHC(CH_3)_2SCH(CH_3)_2 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
984	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH_2COOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
985	$\begin{array}{c} -CH-\text{Cyclohexyl} \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
986	$\begin{array}{c} -CH-\text{Thiophenyl} \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
987	$\begin{array}{c} -CH-\text{p-Fluorophenyl} \\   \\ NHCOOC_2H_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
988	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
989	$\begin{array}{c} -CHCH_2C(CH_3)_3 \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond

Table 1 (continued)

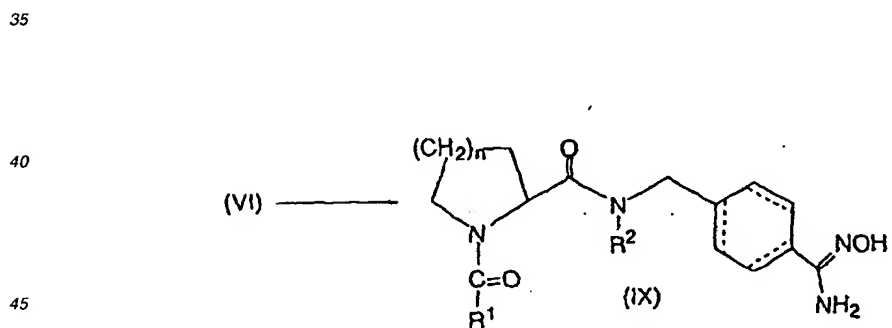
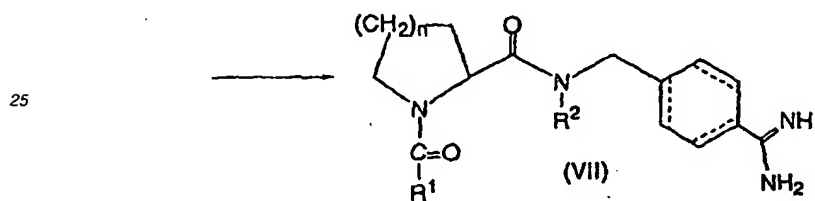
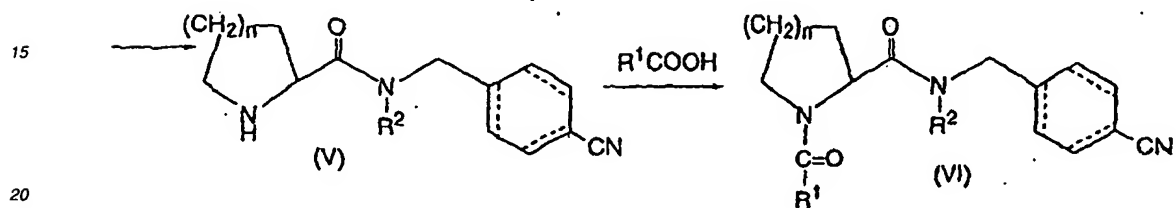
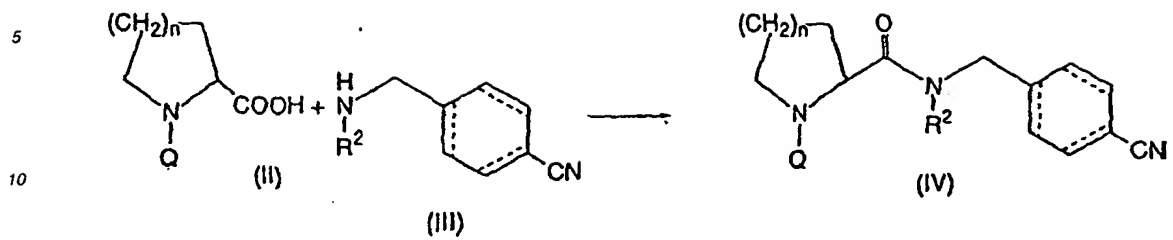
Compound No.	$-R^1 \left( \begin{array}{c} -D-(CH)_m-E-R^4 \\   \\ R^5 \end{array} \right)$	$-R^2$	$-R^3$	n	A	Broken line
990	$\begin{array}{c} -CHCH_2-\text{C}_6\text{H}_5 \\   \\ NHCON(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
991	$\begin{array}{c} -CHCH_2COOC(CH_3)_3 \\   \\ NHCOOCH_2-\text{C}_6\text{H}_5 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	Single bond
992	$\begin{array}{c} -CHCH_2OH \\   \\ NHCOOC(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
993	$\begin{array}{c} -CHCH(CH_3)OC(CH_3)_3 \\   \\ NHCOOCH(CH_3)_2 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
994	$\begin{array}{c} -CH-\text{C}_6\text{H}_{11} \\   \\ OCOCH_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—
995	$\begin{array}{c} -CHCH_2O-\text{C(CH}_3\text{)}_2\text{C}_4\text{H}_8 \\   \\ NHCOOCH(CH_3)_3 \end{array}$	-H	$\begin{array}{c} NOH \\ // \\ -C \\   \\ NH_2 \end{array}$	1	C	—

1003	$\begin{array}{c} -CHCH_2OC(CH_3)_3 \\   \\ NHCOOC_2H_5 \end{array}$	-H	$-NH_2$	1	C	—
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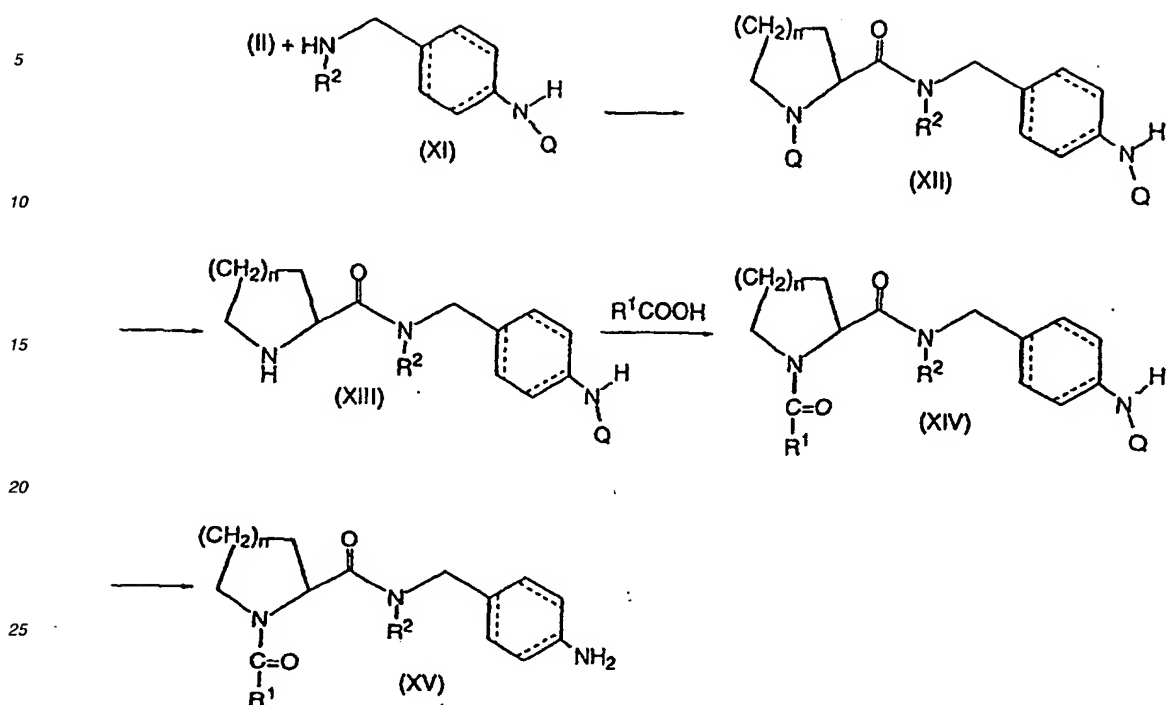
[0019] Hereinafter, the production process for the compounds of the present invention will be explained.

[0020] The compounds of the present invention can be produced through any combination of reactions suitable for the objective compounds. Typical reaction schemes will be shown below, but they should not be construed to be limiting the scope of the present invention.

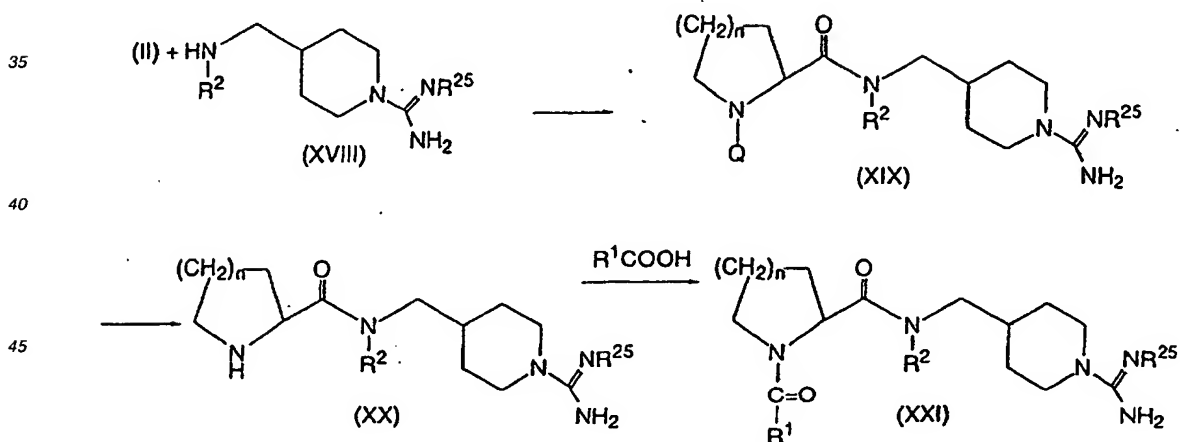
## (Reaction scheme I)



## (Reaction scheme II)



## (Reaction scheme III)



wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^{25}$ ,  $n$  and broken line are as defined above; Q is an aminoprotecting group, such as benzyloxycarbonyl group, tertiary butyloxycarbonyl group, etc.; Z is a leaving group such as halogen atom, methanesulfonyloxy group, toluenesulfonyloxy group, trifluoromethylsulfonyloxy group, acetoxy (acetyloxy) group, etc.

[0021] In the above reaction schemes, a known method for synthesizing amide can be used for synthesizing the compounds (IV), (VI), (XII), (XIV), (XIX) and (XXI). There are various conventional methods, for example, a method using dehydrating agents such as dicyclohexylcarbodiimide, 1-ethyl-3-(dimethylaminopropyl)carbodiimide, carbonyl-diimidazole, etc., azido method, acid halide method, acid anhydride method, active ester method and the like (e.g., see, "JIKKEN KAGAKU KOZA, 22, YUKI-GOSEI IV", pp. 259 - (1992), ed. "JAPAN Chemical Society", 4th. edition,

published by Maruzen). The reaction is conducted under cooling or heating (or at room temperature) using an inert solvent such as tetrahydrofuran, diethyl ether, dichloromethane, etc. in a conventional manner. In the above schemes, the compounds (V), (XIII), (XV) and (XX) can be synthesized by deprotection according to a method known in the peptide chemistry (e.g. see "The Principle and Experimental Procedures of Peptide Synthesis" written by Nobuo IZUMIYA et al., published by Maruzen).

[0022] Further, the compound (VII) is synthesized by reacting imidate, which is obtained by reacting the compound (VI) with alcohol and an inorganic acid such as hydrochloric acid, with ammonia or an ammonium salt; or by reacting a thioamide compound, which is obtained by reacting the compound (VI) with hydrogen sulfide in the presence of an organic base such as triethylamine, pyridine, etc., with a lower alkylhalogen compound such as methyl iodide, etc., followed by reacting the resulting thioimide compound with ammonia or an ammonium salt. Further, the compound (IX) is synthesized by reacting the compound (VI) with hydroxylamine or acid adduct thereof in a suitable solvent such as water, alcohol, tetrahydrofuran, etc. at room temperature or under heating.

[0023] The respective compounds thus obtained can be isolated and purified by conventional chemical procedures such as extraction, crystallization, recrystallization, various chromatography and the like.

[0024] When the compounds of the present invention are used for clinical application, a proportion of a therapeutically active ingredient to a carrier component varies within a range of 1 to 90% by weight. For example, the compounds of the present invention may be orally administered in the dosage form such as granules, fine granules, powders, tablets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or intravenously, intramuscularly or subcutaneously administered in the form of injections. Further, they may also be used in the form of suppositories. They may also be formed into powders which can be converted into solutions or the like for injection before use. There can be used pharmaceutical organic or inorganic solid or liquid carriers or diluents which are suitable for oral, intestinal or parenteral administration for preparing the drugs of the present invention. As the excipient used for preparing solid preparations, for example, there can be used lactose, sucrose, starch, talc, cellulose, dextrin, kaoline, calcium carbonate and the like. Liquid preparations for oral administration, i.e. emulsions, syrups, suspensions, solutions, etc. contain inert diluents which are normally used, e.g. water, vegetable oil, etc. This preparation can contain adjuvants such as humectants, suspension auxiliary agents, sweeteners, aromatics, colorants, preservatives, etc., in addition to inert diluents. The resulting liquid preparations may be contained in a capsule of an absorbable substance such as gelatin. As the solvent or suspending agent used for preparing preparations for parenteral administration, i.e. injections, suppositories, etc., for example, there can be used water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. As the base used for preparing suppositories, for example, there can be used cacao butter, emulsified cacao butter, laurin tallow, witepsol and the like. Preparations may be prepared by a conventional method.

[0025] The clinical dose varies depending upon age, pathology, condition of diseases and the like. For example, in the case of administering orally to an adult patient, the compounds of the present invention are normally administered with a daily dose of about 0.01 to 1000 mg, preferably 10 to 1000 mg. The pharmaceutical composition of the present invention may be administered 1 to 3 times per day or administered intermittently with the above daily dose.

[0026] When using as injections, it is advantageous that the compounds of the present invention are administered continuously or intermittently to an adult patient with a single dose of 0.001 to 100 mg.

[0027] The prolineamide derivatives of the present invention or the salts thereof have a strong inhibition activity to proteases such as thrombin, trypsin and the like. The compounds of the present invention are also superior in oral absorptive action so that they are useful as oral antithrombin agents, i.e. oral anticoagulants, or oral antitrypsin agents, i.e. remedy for pancreas diseases such as pancreatitis.

[0028] The following Examples and Experimental Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

[0029] The conventional abbreviations used in Examples are as follows: THF: tetrahydrofuran, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide, CDI: carbonyldiimidazole, DPPA: diphenylphosphoryl azide, Z: benzyloxycarbonyl, Boc: tertiary butyloxycarbonyl.

[0030] Further, NMR in physical properties stands for a nuclear magnetic resonance spectrum and the numeral is  $\delta$  value in ppm, which is conventionally used for indicating the chemical shift. TMS (tetramethylsilane) was used as the internal standard. Further, the numeral shown in parenthesis following  $\delta$  value is the number of hydrogen atoms, and the indications following the number of hydrogen atoms mean that s is singlet, d is doublet, t is triplet, q is quartet, m is multiplet, br is broad absorption peak, respectively.

[0031] IR stands for an infrared spectrum and measured as potassium bromide tablets unless otherwise stated. The numerical means the wave number in  $\text{cm}^{-1}$ .

[0032] Only main absorption peak was shown. Further, mp means the non-corrected melting point in  $^{\circ}\text{C}$ .

#### Reference Example 1

[0033] Synthesis of 4-amidino-[(S)-N-((R)-2-methylsulfonylaminocyclohexylacetyl) prolyl]aminomethylbenzene

(Reference compound No. 105 of Table 1) hydrochloride.

(a) N-4-cyanobenzylphthalimide

5 [0034] To a solution of potassium phthalimide (76 g, 410 mmol) in DMF (250 ml), a solution of 4-cyanobenzyl bromide (73 g, 373 mmol) in THF (250 ml) is added and stirred at 50°C for 3 hours.

[0035] Water (500 ml) is added to the mixture and a precipitated crystal was collected. Then, the crystal is washed with water and dried to give 96 g of the titled compound (99%). mp: 189-191°C.

10 (b) 4-Cyano-[(S)-prolyl]aminomethylbenzene hydrochloride

[0036] To a solution of the compound (39 g, 150 mmol) obtained in the item (a) in methanol (250 ml), hydrazine hydrate (9 ml) is added and refluxed for 6 hours. After the solvent is evaporated, an aqueous 40% sodium hydroxide solution (300 ml) is added to the residue and stirred.

15 [0037] The reaction mixture is extracted with toluene and the organic layer is washed once with water and saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting crude product (15 g, 73%) is used for the next step.

[0038] To a solution of (S)-N-Boc-proline (23.7 g, 110 mmol) in THF (250 ml), CDI (17.8 g, 110 mmol) is added at 0°C.

20 [0039] After the reaction solution is stirred for 2 hours, a solution of the crude product obtained in the above reaction in THF (150 ml) is added. After stirring for 6 hours, the solvent is evaporated and water (300 ml) is added to the residue. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (hexane-ethyl acetate).

25 [0040] The resulting oily product is dissolved in ethyl acetate (100 ml) and a 4N-hydrochloride in ethyl acetate (69 ml) is added and the mixture is stirred at 0°C for 3 hours. The precipitated white solid is collected, washed with ethyl acetate and dried under reduced pressure to give 25.9 g of the titled compound (89%).

NMR (DMSO-d<sub>6</sub>)

1.80-1.96 (m, 3H), 2.30-2.40 (m, 1H), 3.21 (br, 2H), 4.26 (br, 1H), 4.44 (d, 2H), 7.49 (d, 2H), 7.82 (d, 2H), 8.59 (br, 1H), 9.39 (t, 1H), 10.07 (br, 1H)

30

(c) 4-Cyano-[(S)-N-((R)-2-t-butyloxycarbonylamino-cyclohexylacetyl) prolyl]aminomethylbenzene

35 [0041] To a solution of the product (21 g, 79 mmol) obtained in the item (b) and (R)-N-t-butyloxycarbonylcyclohexylglycine (20.4 g, 79 mmol) in DMF (200 ml), a solution of triethylamine (22 ml, 159 mmol) and DPPA (22 g, 79 mmol) in DMF (50 ml) is added at 0°C. The mixture is allowed to stand at room temperature and then stirred for 12 hours. Water (400 ml) is added to the reaction mixture which is extracted with toluene-ethyl acetate (1:2). The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. After the solvent is evaporated, the residue is purified with silica gel chromatography (chloroform-methanol) to give 26.7 g of the titled compound (72%).

40 NMR (CDCl<sub>3</sub>)

1.01-1.43 (m, 15H), 1.65-2.38 (m, 9H), 3.57 (q, 1H), 3.96-4.06 (m, 2H), 4.47 (dq, 2H), 4.69 (d, 1H), 5.12 (d, 1H), 7.35 (d, 2H), 7.59 (d, 2H), 7.73 (t, 1H)

45

(d) 4-Cyano-[(S)-N-((R)-2-methylsulfonylamino-cyclohexylacetyl)prolyl] aminomethylbenzene

50 [0042] To a solution of the compound (26.7 g, 57 mmol) obtained in the item (c) in chloroform (50 ml), a 4-N hydrochloride in ethyl acetate (30 ml) is added at 0 °C. The mixture is stirred for 3 hours and then the solvent is evaporated. The resulting residue was dissolved in dichloromethane (250 ml) and triethylamine (19 ml) is added. Then, a solution of methanesulfonyl chloride (7.9 g, 68 mmol) in dichloromethane (50 ml) is added at 0°C and the mixture is stirred for 3 hours. The organic layer is washed once with a saturated sodium bicarbonate solution, water and saturated brine, successively, and then dried over sodium sulfate. The resulting residue is purified with silica gel chromatography (hexane-ethyl acetate) to give 18.6 g of the titled compound (73%).

NMR (CDCl<sub>3</sub>)

55 0.9-1.29 (m, 5H), 1.60-1.85 (m, 5H), 2.0-2.4 (m, 5H), 2.89 (s, 3H), 3.55 (q, 1H), 3.80-3.88 (m, 2H), 4.43 (d, 2H), 4.61 (d, 2H), 5.60 (d, 2H), 7.31 (t, 1H), 7.37 (d, 2H), 7.60 (d, 2H)

(e) 4-Amidino-[(S)-N-((R)-2-methylsulfonylamino-cyclohexylacetyl) prolyl]aminomethylbenzene chloride

**[0043]** To a solution of the compound (18.6 g, 42 mmol) obtained in the item (d) in chloroform (100 ml), a 37% hydrochloride in ethanol (100 ml) is added at 0°C. The mixture is allowed to stand at 0°C for 48 hours and then the solvent is evaporated. The resulting residue is dissolved in methanol (100 ml) and ammonium carbonate (16 g, 166 mmol) is added at 0°C. After stirring for 6 hours, the solvent is evaporated and the resulting residue is purified with silica gel chromatography (chloroform-methanol) to give 5.2 g of the titled compound (73%).

NMR (DMSO-d<sub>6</sub>)

9.39 (br, 4H), 8.66 (t, 1H), 7.81 (d, 2H), 7.48 (d, 2H), 7.40 (m, 1H), 4.47-4.14 (m, 3H), 3.90 (m, 1H), 3.71 (m, 1H), 3.59 (m, 1H), 2.79 (s, 3H), 2.13 (m, 1H), 1.88 (m, 3H), 1.69-1.53 (m, 5H), 1.14 (m, 6H)

IR: 3366, 2930, 2855, 1636, 1541, 1489, 1451, 1152

**[0044]** According to the same procedures described above, the compounds shown in the following Examples were synthesized.

#### Example 1

**[0045]** 4-Amidino-[(S)-N-((R)-N'-formylphenylalanyl) prolyl] aminomethylbenzene (compound No. 94 of Table 1) hydrochloride NMR (DMSO-d<sub>6</sub>)

9.56 (br, 2H), 9.36 (br, 2H), 8.97 (t, 1H), 8.70 - 8.60 (m, 1H), 7.86 (d, 1H), 7.83 (d, 2H), 7.46 (d, 2H), 7.37-7.17 (m, 5H), 4.36-4.16 (m, 4H), 3.60 - 2.70 (m, 4H), 2.40-1.20 (m, 4H)

IR: 3370, 1647, 1541, 1489, 1454, 1404, 704

#### Example 2

**[0046]** 4-Amidino-[(S)-N-((R)-2-ethoxycarbonylamino-3-methyl-3-methylthiobutanoyl) prolyl]aminomethylbenzene (compound No. 98 of Table 1) hydrochloride NMR (DMSO-d<sub>6</sub>)

8.89 (br, 2H), 8.66 (br, 2H), 7.77 (d, 2H), 7.33 (d, 2H), 6.27 (d, 1H), 4.65 (m, 1H), 4.46 (d, 1H), 4.37 (m, 2H), 3.97-3.72 (m, 4H), 2.62 (m, 1H), 2.15 (br, 3H), 2.04 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.05 (t, 3H)

IR: 3323, 2926, 1635, 1535, 1439, 1242, 1055

#### Example 3

**[0047]** 4-Amidino-[(S)-N-(4-phenylbutanoyl)prolyl] aminomethylbenzene (compound No. 3 of Table 1) hydrochloride NMR (DMSO-d<sub>6</sub>)

9.39 (br, 2H), 9.22 (br, 2H), 8.55 (t, 1H), 7.80 (d, 2H), 7.48 (d, 2H), 7.31-7.13 (m, 5H), 4.37-4.30 (m, 3H), 3.60-3.30 (m, 2H), 2.60 (t, 2H), 2.34-1.75 (m, 8H)

IR: 3264, 1618, 1541, 1491, 1451, 702

#### Example 4

**[0048]** 4-Amidino-[(S)-N-(2-benzyloxyacetyl)prolyl] aminomethylbenzene (compound No. 55 of Table 1) hydrochloride NMR (DMSO-d<sub>6</sub>)

9.41 (br, 2H), 9.23 (br, 2H), 8.66 (t, 1H), 7.80 (d, 2H), 7.49 (d, 2H), 7.42-7.27 (m, 5H), 4.61-4.08 (m, 7H), 3.56-3.40 (m, 2H), 2.20-1.78 (m, 4H)

IR: 3262, 1645, 1539, 1489, 1454, 740

#### Example 5

**[0049]** Trans-4-amidino-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl)prolyl] aminomethylcyclohexane (compound No. 263 of Table 1) hydrochloride

(a) Trans-4-N-benzyloxycarbonylamino-methyl-cyclohexylnitrile

**[0050]** To a solution of trans-4-aminomethylcyclohexanecarboxylic acid (25 g, 159 mmol) and sodium carbonate (20 g, 191 mmol) in water (300 ml), benzyloxycarbonyl chloride (27 ml, 190 mmol) is added at 0°C. After stirring for 6 hours, 1N-hydrochloric acid is added until the pH of the reaction mixture indicates 2, and the precipitated white solid is col-



lected, washed with water and dried. The resulting white solid is dissolved in THF (300 ml) and CDI (21 g, 130 mmol) is added at 0°C. After stirring for 3 hours, the reaction mixture is added dropwise to a mixed solution of 33% ammonia in water (50 ml) and THF (150 ml) at 0°C. After stirring for 5 hours, the solvent is evaporated and water (500 ml) is added, and the precipitated white solid is collected, washed with water and dried.

[0051] To a solution of the resulting compound in 1,2-dichloroethane (500 ml), thionyl chloride (19 ml, 260 mmol) is added and heated to an inner temperature of 70°C. After stirring for 5 hours, the reaction mixture is poured into ice water and neutralized with an aqueous 1N-sodium hydroxide solution. After extracting with chloroform, the organic layer is washed twice with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting crude product is recrystallized (hexane-ethyl acetate) to give 22.8 g of the titled compound (53%). mp: 90-92°C

(b) Trans-4-(S)-prolylaminomethyl-cyclohexylnitrile

[0052] The compound obtained in the item (a) is dissolved in ethanol (250 ml) and the catalytic hydrogenation is conducted at room temperature and atmospheric pressure in the presence of palladium black (1 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

[0053] To a solution of (S)-N-benzyloxycarbonylproline (20.7 g, 83 mmol) in THF (150 ml), CDI (13.5 g, 83 mmol) is added at 0°C. After stirring for 3 hours, a solution of the compound obtained in the above reaction in THF (200 ml) is added at 0°C. After stirring for 12 hours, the solvent is evaporated, and chloroform (400 ml) is added to the resulting residue. The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting residue is purified with silica gel chromatography (chloroform-methanol).

[0054] The resulting compound is dissolved in ethanol (250 ml) and the catalytic hydrogenation is conducted at room temperature and atmospheric pressure in the presence of palladium black (1 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated to give 18.8 g of the titled compound (95%).

NMR (DMSO-d<sup>6</sup>)

0.88-1.06 (m, 2H), 1.38-1.52 (m, 3H), 1.68-2.03 (m, 7H), 2.20-2.40 (m, 1H), 2.52-2.67 (m, 1H), 2.80-3.20 (m, 4H), 4.03-4.10 (m, 1H), 7.53 (br, 1H), 8.65-8.70 (m, 1H)

(c) Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane hydrochloride

[0055] According to the same manner as that described in the items (c) to (e) of Example 1, the titled compound can be synthesized from the compound obtained in the item (b) and (R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoic acid.

NMR (DMSO-d<sup>6</sup>)

8.95 (br, 2H), 8.69 (br, 2H), 7.60 (br, 1H), 6.32 (br, 1H), 4.56 (m, 1H), 4.39 (m, 1H), 4.18 (q, 2H), 4.10 (m, 1H), 3.52 (m, 1H), 3.19 (m, 1H), 2.89 (m, 1H), 2.69 (m, 1H), 2.14-1.59 (m, 12H), 1.26 (t, 3H), 0.98 (s, 9H), 0.98-0.89 (m, 2H)  
IR: 3314, 2954, 1686, 1639, 1543, 1449, 1250, 1059

[0056] According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 6

[0057] Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminoethylcyclohexane (compound No. 227 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.93 (br, 2H), 8.81 (br, 2H), 7.53 (br, 1H), 7.38 (t, 1H), 4.50-4.15 (m, 1H), 4.10-3.90 (m, 2H), 3.73-3.17 (m, 2H), 3.05-2.80 (m, 3H), 2.39 (br, 1H), 2.00-0.68 (m, 29H)  
IR: 3297, 2926, 2853, 1684, 1543, 1449, 1262, 1053

Example 7

[0058] Trans-4-amidino-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 265 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.91 (br, 2H), 8.78 (br, 2H), 7.55 (br, 1H), 7.28 (t, 1H), 4.78-4.70 (m, 1H), 4.30-3.92 (m, 1H), 3.80-3.20 (m, 3H), 3.0-2.75 (m, 2H), 2.50-1.37 (m, 14H), 1.18-1.00 (m, 6H), 1.0-0.81 (m, 1H)  
IR: 3285, 2953, 2870, 1684, 1541, 1449, 1250, 1111

## Example 8

**[0059]** Trans-4-amidino-[(S)-N-((R)-2-isopropoxycarbonylamino-2-cyclohexylacetyl) propyl]aminomethylcyclohexane (compound No. 228 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.91 (br, 2H), 8.69 (br, 2H), 7.36 (br, 1H), 5.99 (d, 1H), 4.84-4.79 (m, 1H), 4.58 (br, 2H), 4.53-4.50 (m, 2H), 4.10-3.90 (m, 2H), 3.60-3.40 (m, 1H), 2.50-0.97 (m, 30H)

IR: 3297, 2980, 2930, 2855, 1684, 1539, 1451, 1258

## Example 9

**[0060]** Trans-4-amidino-[(S)-N-((R)-2-ethoxycarbonylamino-4-ethyl-hexanoyl) propyl]aminomethylcyclohexane (compound No. 264 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.91 (br, 2H), 8.70 (br, 2H), 7.54 (m, 1H), 6.34 (m, 1H), 4.56 (m, 1H), 4.38 (m, 1H), 4.11 (m, 3H), 3.48 (m, 1H), 3.21 (m, 1H), 2.88 (m, 1H), 2.68 (m, 1H), 2.30-1.19 (m, 18H), 1.26 (t, 3H), 0.96 (m, 2H), 0.86 (t, 6H)

IR: 3279, 2962, 1685, 1639, 1541, 1448, 1257, 1059, 752

## Example 10

**[0061]** Trans-4-amidino-[(S)-N-((R)-2-t-butoxycarbonylamino-4,4-dimethylpentanoyl) propyl]aminomethylcyclohexane (compound No. 266 of Table 1) glycolate

NMR (DMSO-d<sub>6</sub>)

9.54 (br, 2H), 8.72 (br, 2H), 7.54 (br, 1H), 7.01 (t, 1H), 4.60-4.00 (m, 4H), 3.40 (m, 2H), 3.10-2.75 (m, 3H), 2.35 (br, 1H), 2.00-1.20 (m, 24H), 0.91 (s, 9H)

IR: 3316, 2953, 1686, 1543, 1449, 1368, 1167

## Example 11

**[0062]** 4-[(S)-N-((R)-2-t-butyloxycarbonylamino-cyclohexylacetyl) propyl] aminomethyl-benzamidoxime (compound No. 396 of Table 1)

**[0063]** To a solution of the compound (0.94 g, 2 mmol) obtained in the item (c) of Example 1 in ethanol (15 ml), a solution of sodium carbonate (0.17 g, 1.6 mmol) in water (3 ml) and hydroxyamine hydrochloride (0.22 g, 3.2 mmol) are added. After the reaction mixture is heated at reflux for 8 hours, the solvent is evaporated and the resulting residue is purified with silica gel column chromatography (chloroform-methanol) to give 0.84 g of the titled compound (84%).

NMR (CDCl<sub>3</sub>)

1.0-1.49 (m, 14H), 1.5-2.4 (m, 10H), 3.56 (br, 1H), 3.97 (br, 1H), 4.09 (t, 1H), 4.41 (dq, 2H), 4.67 (d, 1H), 4.94 (br, 2H), 5.41 (d, 1H), 7.20 (d, 2H), 7.23-7.27 (m, 1H), 7.50 (d, 2H), 7.75 (br, 1H)

IR: 3345, 2978, 2930, 2855, 1640, 1528, 1449, 1167

**[0064]** According to the same procedures, the compounds shown in the following Examples were synthesized.

## Example 12

**[0065]** 4-[(S)-N-phenylacetylpropyl] aminomethyl-benzamidoxime (compound No. 374 of Table 1)

NMR (CDCl<sub>3</sub>)

8.11 (t, 1H), 7.37 (d, 2H), 7.28-7.23 (m, 5H), 7.08 (d, 2H), 4.88 (s, 2H), 4.68 (d, 1H), 4.51 (m, 1H), 4.21 (m, 1H), 3.71 (s, 2H), 3.63-3.51 (m, 2H), 2.40-2.01 (m, 4H)

IR: 3315, 2968, 1637, 1543, 1244, 1155, 927, 709

## Example 13

**[0066]** 4-[(S)-N-((R)-N'-ethoxycarbonylphenylalanyl) propyl]aminomethylbenzamidoxime (compound No. 387 of Table 1)

NMR (CDCl<sub>3</sub>)

7.54 (d, 2H), 7.27-7.19 (m, 7H), 6.31 (d, 1H), 5.05 (br, 2H), 4.65-4.42 (m, 3H), 4.24-4.10 (m, 1H), 3.80-3.40 (m, 3H), 3.10-2.95 (m, 2H), 2.60-2.50 (m, 1H), 2.14 (br, 1H), 1.95-1.50 (m, 3H), 0.99 (t, 3H)

IR: 3339, 1641, 1539, 1451, 1260, 752, 702

## Example 14

[0067] 4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminomethyl-benzamidoxime (compound No. 397 of Table 1)

NMR (CDCl<sub>3</sub>)

7.75 (br, 1H), 7.50 (d, 2H), 7.21 (d, 2H), 5.40 (d, 1H), 4.94 (br, 2H), 4.64 (br, 1H), 4.40-4.25 (m, 3H), 3.95 (br, 1H), 3.50-3.40 (m, 1H), 2.0-0.80 (m, 26H)

IR: 3337, 2978, 2924, 2851, 1642, 1536, 1449, 1167

## Example 15

[0068] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-3-methyl-3-methylthlobutanoyl] prolyl]aminomethyl-benzamidoxime (compound No. 419 of Table 1)

NMR (CDCl<sub>3</sub>)

7.66 (t, 1H), 7.53 (d, 2H), 7.23 (d, 2H), 5.64 (d, 1H), 4.91 (s, 2H), 4.68 (d, 1H), 4.58-4.30 (m, 3H), 3.90 (m, 1H), 3.87-3.76 (m, 2H), 3.62 (m, 1H), 2.37 (m, 1H), 2.09-2.00 (m, 3H), 2.06 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.09 (t, 3H)

IR: 3339, 2978, 1641, 1535, 1439, 1249, 1057, 929, 754

## Example 16

[0069] 4-[(S)-N-[(R)-phenylalanyl] prolyl]aminomethyl-benzamidoxime (compound No. 390 of Table 1) dihydrochloride

NMR (DMSO-d<sub>6</sub>)

11.24 (br, 1H), 9.02 (br, 2H), 8.91 (t, 1H), 8.80 (br, 3H), 7.66 (d, 2H), 7.44 (d, 2H), 7.35-7.22 (m, 5H), 4.30-4.16 (m, 4H), 3.57-2.95 (m, 3H), 2.45-2.30 (m, 1H), 1.90-1.20 (m, 4H)

IR: 3059, 1649, 1539, 1491, 1454

## Example 17

[0070] Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-2-cyclohexylacetyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 430 of Table 1)

NMR (CDCl<sub>3</sub>)

7.14 (br, 1H), 5.70 (d, 1H), 4.85-4.80 (m, 1H), 4.70-4.50 (m, 3H), 4.17-4.08 (m, 2H), 3.96 (br, 1H), 3.54 (q, 1H), 3.05 (t, 2H), 2.40-2.20 (m, 1H), 2.09-0.88 (m, 30H)

IR: 3342, 2978, 2928, 2855, 1653, 1449, 1256, 1111

## Example 18

[0071] Trans-4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 435 of Table 1)

NMR (CDCl<sub>3</sub>)

7.14 (br, 1H), 5.40 (d, 1H), 4.60-4.33 (m, 5H), 3.88 (br, 1H), 3.43 (q, 1H), 3.20-3.11 (m, 1H), 3.0-2.96 (m, 1H), 2.40-2.30 (m, 1H), 2.0-0.84 (m, 35H)

IR: 3356, 2926, 2853, 1649, 1537, 1448, 1167

## Example 19

[0072] Trans-4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-2-cyclohexylacetyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 433 of Table 1)

NMR (CDCl<sub>3</sub>)

7.15 (br, 1H), 5.28 (d, 1H), 4.58 (br, 4H), 4.09 (t, 1H), 3.92 (br, 1H), 3.53 (q, 1H), 3.20-2.90 (m, 2H), 2.40 (br, 1H), 2.10-0.91 (m, 33H)

IR: 3347, 2930, 2855, 1649, 1541, 1451, 1169

## Example 20

[0073] Trans-4-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 461 of Table 1)

NMR (CDCl<sub>3</sub>)

7.06 (t, 1H), 5.56 (d, 1H), 4.57-4.39 (m, 4H), 4.11 (q, 2H), 3.98 (m, 1H), 3.47 (m, 1H), 3.05 (m, 2H), 2.39 (m, 1H), 2.04-1.78 (m, 10H), 1.57 (d, 2H), 1.56-1.12 (m, 2H), 1.24 (t, 3H), 0.99 (s, 9H), 0.99-0.89 (m, 2H)  
IR: 3356, 2934, 1649, 1541, 1446, 1249, 1059, 927

#### Example 21

**[0074]** Trans-4-[(S)-N-[(R)-2-methoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 458 of Table 1)

NMR (CDCl<sub>3</sub>)

7.04 (t, 1H), 5.53 (d, 1H), 4.68 (s, 2H), 4.56 (d, 1H), 4.43 (m, 1H), 3.98 (m, 1H), 3.66 (s, 3H), 3.47 (m, 1H), 3.07 (m, 2H), 2.39 (m, 1H), 2.19-1.77 (m, 8H), 1.57 (d, 2H), 1.55-1.25 (m, 4H), 0.99 (s, 9H), 0.93 (m, 2H)  
IR: 3344, 2949, 1712, 1649, 1548, 1448, 1249, 1059

#### Example 22

**[0075]** Trans-4-[(S)-N-[(R)-2-t-butoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 467 of Table 1)

NMR (CDCl<sub>3</sub>)

7.12 (t, 1H), 5.14 (d, 1H), 4.58 (d, 1H), 4.53 (s, 2H), 4.37 (m, 1H), 3.92 (m, 1H), 3.45 (m, 1H), 3.19 (m, 1H), 2.95 (m, 1H), 2.42 (m, 1H), 2.06-1.79 (m, 8H), 1.53 (d, 2H), 1.52-1.34 (m, 4H), 1.43 (s, 9H), 0.99 (s, 9H), 1.00-0.89 (m, 2H)  
IR: 3358, 2930, 1649, 1535, 1448, 1367, 1249, 1168

#### Example 23

**[0076]** Trans-4-[(S)-N-[(R)-2-benzyloxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 469 of Table 1)

NMR (CDCl<sub>3</sub>)

7.36-7.27 (m, 5H), 7.04 (t, 1H), 5.63 (d, 1H), 5.16-5.00 (m, 2H), 4.58-4.46 (m, 4H), 3.97 (m, 1H), 3.47 (m, 1H), 3.06-2.92 (m, 2H), 2.43-2.38 (m, 1H), 2.01-1.72 (m, 8H), 1.58 (d, 2H), 1.50-1.23 (m, 4H), 0.98 (s, 9H), 0.98-0.88 (m, 2H)  
IR: 3356, 2928, 1649, 1541, 1448, 1249, 1053 929

#### Example 24

**[0077]** Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 464 of Table 1)

NMR (CDCl<sub>3</sub>)

7.11 (t, 1H), 5.49 (d, 1H), 4.83 (m, 1H), 4.56 (m, 3H), 4.42 (dd, 1H), 3.98 (m, 1H), 3.47 (dd, 1H), 3.04 (m, 2H), 2.40 (m, 1H), 2.01 (m, 2H), 1.92 (m, 3H), 1.80 (m, 3H), 1.57 (d, 2H), 1.39 (m, 4H), 1.21 (m, 6H), 0.99 (s, 9H), 0.94 (m, 2H)  
IR: 3343, 1649, 1541, 1449, 1275

#### Example 25

**[0078]** Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-2-cyclopentylacetyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 429 of Table 1)

NMR (CDCl<sub>3</sub>)

7.14 (t, 1H), 5.42 (d, 1H), 4.83 (m, 1H), 4.60 (d, 1H), 4.52 (s, 2H), 4.13 (m, 1H), 3.98 (m, 1H), 3.56 (m, 1H), 3.04 (m, 2H), 2.35 (m, 1H), 2.24 (m, 1H), 2.10-1.30 (m, 20H), 1.23 (dd, 6H), 1.01-0.93 (m, 2H)  
IR: 3344, 2934, 1649, 1541, 1448, 1275, 1111, 754

#### Example 26

**[0079]** Trans-4-[(S)-N-[(R)-2-t-butoxycarbonylamino-2-cyclopentylacetyl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 432 of Table 1)

NMR (CDCl<sub>3</sub>)

7.16 (t, 1H), 5.16 (d, 1H), 4.60 (d, 1H), 4.51 (s, 2H), 4.14 (t, 1H), 3.94 (m, 1H), 3.52 (m, 1H), 3.01 (m, 2H), 2.38 (m, 1H), 2.23-1.39 (m, 21H), 1.43 (s, 9H), 1.17-0.90 (m, 2H)  
IR: 3350, 2932, 1649, 1541, 1448, 1367, 1251, 1167, 929

## Example 27.

**[0080]** Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-3-cyclohexylpropanoyl) propyl]aminomethylcyclohexanecarboxamidoxime (compound No. 428 of Table 1)

NMR (CDCl<sub>3</sub>)

7.08 (br, 1H), 5.53 (d, 1H), 4.80-4.40 (m, 4H), 4.10-3.85 (m, 4H), 3.44 (q, 1H), 3.06 (t, 3H), 2.15-0.90 (m, 29H)  
IR: 3343, 2926, 2853, 1649, 1541, 1449, 1260, 1053

## Example 28

**[0081]** Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-3-cyclohexylpropanoyl) propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 431 of Table 1)

NMR (CDCl<sub>3</sub>)

7.12 (br, 1H), 5.51 (d, 1H), 4.85-4.70 (m, 1H), 4.60-4.30 (m, 4H), 4.0-3.85 (m, 1H), 3.44 (q, 1H), 3.10-2.95 (m, 3H), 2.45-2.35 (m, 1H), 2.05-0.80 (m, 32H) IR: 3347, 2978, 2926, 2853, 1649, 1539, 1449, 1261, 1111

## Example 29

**[0082]** Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-4-ethyl-hexanoyl) propyl]aminomethylcyclohexanecarboxamidoxime (compound No. 463 of Table 1)

NMR (CDCl<sub>3</sub>)

7.11 (t, 1H), 5.41 (d, 1H), 4.83 (m, 1H), 4.56 (m, 3H), 4.39 (m, 1H), 3.94 (m, 1H), 3.46 (m, 1H), 3.02 (m, 2H), 2.39 (m, 1H), 2.10-1.20 (m, 20H), 1.22 (dd, 6H), 1.02-0.84 (m, 2H), 0.86 (t, 6H)  
IR: 33346, 2962, 2930, 1653, 1541, 1448, 1271, 1113

## Example 30

**[0083]** Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-4-ethyl-hexanoyl) propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 466 of Table 1)

NMR (CDCl<sub>3</sub>)

7.19 (t, 1H), 5.14 (d, 1H), 4.60 (d, 1H), 4.50 (s, 2H), 4.33 (m, 1H), 3.89 (m, 1H), 3.43 (m, 1H), 3.15 (m, 1H), 2.95 (m, 1H), 2.40 (m, 1H), 2.10-1.19 (m, 20H), 1.43 (s, 9H), 1.04-0.89 (m, 2H), 0.86 (t, 6H)  
IR: 3346, 2964, 2930, 1649, 1541, 1448, 1367, 1280, 1251, 1168, 929

## Example 31

**[0084]** Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-heptanoyl) propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 459 of Table 1)

NMR (CDCl<sub>3</sub>)

7.08 (t, 1H), 5.60 (d, 1H), 4.58 (m, 3H), 4.35 (m, 1H), 4.07 (m, 2H), 3.92 (m, 1H), 3.48 (m, 1H), 3.06 (m, 2H), 2.40 (m, 1H), 2.04-1.32 (m, 20H), 1.24 (t, 3H), 0.89 (t, 3H), 0.98 (m, 2H)  
IR: 3346, 2928, 1649, 1541, 1448, 1255, 1055, 927

## Example 32

**[0085]** Trans-4-[(S)-N-((R)-N'-t-butoxycarbonylamino-methionyl) propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 468 of Table 1) NMR (CDCl<sub>3</sub>)

7.07 (m, 1H), 5.31 (d, 1H), 4.55 (m, 4H), 3.56 (m, 1H), 3.10 (m, 2H), 2.57 (t, 2H), 2.37 (m, 1H), 2.11 (s, 3H), 2.06-1.29 (m, 14H), 1.43 (s, 9H), 1.00 (m, 2H)  
IR: 3354, 2928, 1647, 1541, 1448, 1367, 1251, 1167

## Example 33

**[0086]** Trans-4-[(S)-N-((R)-2-hydroxy-4,4-dimethyl-pentanoyl) propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 454 of Table 1)

NMR (CDCl<sub>3</sub>)

7.19 (t, 1H), 4.68 (s, 2H), 4.50 (d, 1H), 4.36 (t, 1H), 3.64 (t, 1H), 3.39 (m, 1H), 3.06 (m, 2H), 2.35 (m, 2H),

2.16-1.79 (m, 9H), 1.44 (d, 2H), 1.43-1.25 (m, 3H), 1.00-0.95 (m, 2H), 1.02 (s, 9H)  
 IR: 3337, 2944, 1653, 1620, 1566, 1448, 1386, 1248, 1087

#### Example 34

**[0087]** Trans-4-[(S)-N-[(R)-2-ethoxycarbonylamino-4-ethyl-hexanoyl] propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 460 of Table 1)

NMR (CDCl<sub>3</sub>)

7.07 (t, 1H), 5.53 (d, 1H), 4.56 (m, 3H), 4.40 (m, 1H), 4.11 (q, 2H), 3.96 (m, 1H), 3.45 (m, 1H), 3.05 (m, 2H), 2.36 (m, 1H), 2.09-1.77 (m, 10H), 1.61-1.21 (m, 8H), 1.24 (t, 3H), 1.02-0.83 (m, 2H), 0.86 (t, 6H)  
 IR: 3342, 2962, 2930, 1649, 1541, 1448, 1379, 1269, 1059, 929

#### Reference Example 2

**[0088]** Trans-4-amino-[(S)-N-[(R)-N'-methanesulfonylphenylalanyl] propyl] aminomethylcyclohexane (Reference compound No. 776 of Table 1) L-tartrate.

(a) Trans-4-t-butyloxycarbonylamino-benzyloxycarbonylaminoethylcyclohexane

**[0089]** To a solution of trans-4-aminomethylcyclohexanecarboxylic acid (15.7 g, 100 mmol) and sodium hydroxide (4.0 g, 100 mmol) in water (30 ml), benzyloxycarbonyl chloride (15.6 ml, 110 mmol) and sodium hydroxide (4.4 g, 110 mmol) in water (30 ml) are added dropwise at 0°C, simultaneously. After stirring for 4 hours, the mixture is extracted once with ether and 1 N-hydrochloric acid is added to the aqueous layer until the pH of the mixture indicates 2. Then, the precipitated white solid is collected and dried.

**[0090]** To a solution of the resulting compound (12.8 g, 50 mmol) in t-butanol (150 ml), triethylamine (8.3 ml, 60 mmol) and DPPA (13.7 g, 50 mmol) are added and heated at reflux for 8 hours. After the solvent is evaporated, water is added to the residue and the mixture is extracted with chloroform. The organic layer is washed once with an aqueous sodium carbonate (5%), once with an aqueous potassium hydrogensulfate (5%), twice with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chromatography (hexane-ethyl acetate) to give 8.6 g of the titled compound (47%).

NMR (CDCl<sub>3</sub>)

0.85-1.37 (m, 14H), 1.60-1.85 (m, 4H), 2.84 (t, 1H), 3.12 (br, 1H), 5.00 (s, 2H), 6.62 (d, 1H), 7.23-7.39 (m, 6H)

(b) Trans-4-t-butyloxycarbonylamino-[(S)-N-benzyloxycarbonylpropyl] aminomethylcyclohexane

**[0091]** The compound (4.4 g, 12 mmol) obtained in the item (a) is dissolved in methanol (200 ml) and the catalytic hydrogenation is conducted at room temperature and under atmospheric pressure in the presence of palladium black (0.4 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

**[0092]** To a solution of (S)-Z-proline (3.0 g, 12 mmol) in THF (30 ml), CDI (2.0 g, 12 mmol) is added at 0°C. After stirring for 3 hours, a solution of the compound obtained in the above reaction in THF (150 ml) is added at 0°C. After stirring for 6 hours, the solvent is evaporated and water (50 ml) is added to the residue. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (chloroform-methanol) to give 4.2 g of the titled compound (77%).

NMR (CDCl<sub>3</sub>)

0.85-1.06 (m, 4H), 1.44 (s, 9H), 1.60-2.35 (m, 9H), 2.94-3.20 (m, 2H), 3.20-3.55 (m, 3H), 4.31 (br, 1H), 4.47 (br, 1H), 5.14 (s, 2H), 6.90 (br, 1H), 7.15-7.40 (m, 5H)

(c) Trans-4-t-butyloxycarbonylamino-[(S)-N-[(R)-N'-benzyloxycarbonylphenylalanyl] propyl] aminomethylcyclohexane

**[0093]** The compound (3.6 g, 7.9 mmol) obtained in the item (b) is dissolved in methanol (50 ml) and the catalytic hydrogenation is conducted at room temperature and under atmospheric pressure in the presence of palladium black (0.3 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

**[0094]** To a solution of (R)-Z-phenylalanine (2.4 g, 7.9 mmol) in THF (30 ml), CDI (1.3 g, 7.9 mmol) is added at 0°C. After stirring for 4 hours, a solution of the compound obtained in the above reaction in THF (60 ml) is added. After stirring for 8 hours, the solvent is evaporated and water is added to the reaction mixture. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chroma-

topography (chloroform-methanol) to give 4.2 g of the titled compound (89%). NMR (CDCl<sub>3</sub>)

0.85-1.06 (m, 5H), 1.33-2.0 (m, 15H), 2.10-2.22 (m, 1H), 2.50-2.60 (m, 1H), 2.94-3.01 (m, 5H), 3.30 (br, 1H), 3.57 (t, 1H), 4.32-4.59 (m, 3H), 5.08 (d, 2H), 5.69 (d, 1H), 7.02 (br, 1H), 7.18-7.37 (m, 10H)

(d) Trans-4-amino-[(S)-N-[(R)-N'-methanesulfonylphenylalanyl]prolyl] aminomethylcyclohexane L-tartrate.

[0095] The compound (2.4 g, 3.9 mmol) obtained in the item (c) is dissolved in methanol (40 ml) and the catalytic hydrogenation is conducted at room temperature and under atmospheric pressure in the presence of palladium black (0.2 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated. To a solution of the resulting compound in dichloromethane (40 ml), triethylamine (0.65 ml, 4.7 mmol) is added and a solution of methanesulfonyl chloride (0.47 g, 4.1 mmol) in dichloromethane (100 ml) is further added at 0°C. After stirring for 3 hours, an aqueous saturated sodium bicarbonate solution is added and the organic layer is washed once with water and saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (chloroform-methanol),

[0096] The resulting compound is dissolved in chloroform (10 ml) and a 4N-dioxane hydrochloride in dioxane (10 ml) is added at 0°C. After stirring for 2 hours, the solvent is evaporated and chloroform (10 ml) and a 1N-sodium hydroxide solution (10 ml) are added to the residue and, further, the mixture is stirred for 10 minutes. The organic layer is dried over sodium sulfate and a solution of L-tartaric acid (0.34 g, 2.26 mmol) in methanol (5 ml) is added.

[0097] The solvent is evaporated and ether (20 ml) is added, and then the precipitated white solid is collected and dried to give 1.36 g of the titled compound (58%).

NMR (DMSO-d<sub>6</sub>)

7.77 (m, 4H), 7.28 (m, 5H), 4.28 (m, 1H), 4.16 (m, 1H), 3.57-3.45 (m, 8H), 2.73 (s, 3H), 1.91-1.75 (m, 9H), 1.54 (m, 1H), 1.25 (m, 4H), 0.93 (m, 2H)

IR: 3324, 2934, 1734, 1638, 1545, 1453, 1308, 1148

[0098] According to the same procedures, the compounds shown in the following Examples were synthesized.

#### Example 35

[0099] Trans-4-amino-[(S)-N-[(RS)-3-methylsulfonylamino-3-phenylpropanoyl] prolyl]aminomethylcyclohexane (compound No. 777 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.08 (m, 3H), 7.34 (m, 5H), 4.78 (m, 1H), 4.15 (m, 2H), 3.51 (m, 1H), 3.36 (m, 2H), 2.86 (m, 4H), 2.68 (s, 3H), 2.51 (m, 2H), 2.00-1.69 (m, 6H), 1.27 (m, 4H), 0.92 (m, 2H)

IR: 3409, 2936, 1638, 1453, 1314, 1148

#### Example 36

[0100] Trans-4-amino-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 797 of Table 1)

NMR (CDCl<sub>3</sub>)

7.19 (m, 1H), 5.32 (d, 1H), 4.82 (m, 1H), 4.53 (m, 2H), 4.00 (m, 1H), 3.48 (m, 1H), 3.03-2.16 (m, 6H), 2.00-1.81 (m, 6H), 1.57 (d, 2H), 1.49 (m, 4H), 1.24 (m, 6H), 1.00 (s, 9H), 0.95 (m, 2H)

IR: 3326, 2949, 1640, 1541, 1449, 1248

#### Example 37

[0101] Trans-4-amino-[(S)-N-[(R)-N'-ethoxycarbonyl-phenylalanyl] prolyl] aminomethylcyclohexane (compound No. 780 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

7.98 (m, 3H), 7.37 (t, 1H), 7.26 (m, 5H), 4.37 (dd, 1H), 4.16 (m, 1H), 4.02 (m, 2H), 3.88 (m, 1H), 3.59 (m, 1H), 3.43 (m, 1H), 2.86 (m, 5H), 1.93-1.75 (m, 7H), 1.28 (m, 4H), 1.15 (t, 3H), 0.92 (m, 2H)

IR: 3349, 2936, 1642, 1537, 1451, 1258

#### Example 38

[0102] Trans-4-amino-[(S)-[(R)-phenylalanyl] prolyl]aminomethylcyclohexane (compound No. 779 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.69 (br, 3H), 8.09 (br, 4H), 7.37-7.20 (m, 5H), 4.19 (br, 1H), 4.09-4.06 (m, 1H), 3.20-2.82 (m, 5H), 2.0-0.85 (m, 15H)  
IR: 3426, 2936, 1649, 1539, 1497, 1454

5 Example 39

[0103] Trans-4-amino-[(S)-N-[(R)-2-ethoxycarbonyloxy-3-phenylpropanoyl] propyl]aminomethylcyclohexane (compound No. 785 of Table 1) hydrochloride  
NMR (DMSO-d<sup>6</sup>)  
10 7.78 (m, 3H), 7.30 (m, 5H), 7.15 (d, 1H), 5.22 (t, 1H), 4.20 (m, 1H), 4.08 (m, 3H), 3.64 (m, 1H), 3.02-2.88 (m, 5H), 1.92-1.72 (m, 7H), 1.20-0.94 (m, 9H)  
IR: 3397, 2938, 1740, 1655, 1453, 1269

15 Example 40

[0104] Trans-4-amino-[(S)-N-[(R)-2-allylcarbamoyloxy-3-phenylpropanoyl] propyl]aminomethylcyclohexane (compound No. 787 of Table 1) hydrobromide  
NMR (DMSO-d<sup>6</sup>)  
20 7.90 (m, 3H), 7.30 (m, 5H), 7.14 (m, 1H), 5.72 (m, 2H), 5.06 (m, 2H), 4.76 (m, 1H), 4.17 (m, 1H), 3.60 (m, 1H), 2.98-2.85 (m, 5H), 1.87-1.70 (m, 7H), 1.23 (m, 7H), 0.90 (m, 2H)  
IR: 3364, 2936, 1707, 1645, 1543, 1454, 1256

Example 41

25 [0105] Trans-4-amino-[(S)-N-[(R)-2-hydroxy-2-cyclohexylacetyl] propyl] aminomethylcyclohexane (compound No. 768 of Table 1) hydrochloride  
NMR (DMSO-d<sup>6</sup>)  
8.21 (br, 3H), 7.95 (m, 1H), 4.53 (m, 1H), 4.18 (d, 1H), 3.95 (m, 1H), 3.07 (m, 3H), 2.18-1.55 (m, 22H), 1.30-1.03 (m, 2H)  
30 IR: 3422, 2928, 2854, 1637, 1450, 1388, 1240, 1114, 1045

Example 42

[0106] Trans-4-amino-[(S)-N-[(R)-2-hydroxy-2-phenylacetyl] propyl] aminomethylcyclohexane (compound No. 783 of Table 1) hydrochloride  
NMR (DMSO-d<sup>6</sup>)  
7.98 (br, 3H), 7.37-7.28 (m, 5H), 5.48 (br, 1H), 5.23 (d, 1H), 4.23 (d, 1H), 3.70-3.35 (m, 2H), 3.0-2.80 (m, 4H), 2.0-1.60 (m, 8H), 1.40-0.90 (m, 5H)  
IR: 3329, 2935, 1667, 1626, 1552, 1448

40 Example 43

[0107] Trans-4-amino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] propyl]aminomethylcyclohexane (compound No. 794 of Table 1)  
NMR (CDCl<sub>3</sub>)  
45 7.16 (m, 1H), 5.68 (d, 1H), 4.53 (d, 1H), 4.38 (m, 1H), 4.10 (q, 2H), 4.01 (m, 1H), 3.46-3.07 (m, 4H), 2.30-1.81 (m, 8H), 1.58 (m, 5H), 1.26 (t, 3H), 1.00 (s, 9H), 0.95 (m, 2H)  
IR: 3329, 2949, 1642, 1541, 1447, 1248, 1059

[0108] According to the same procedure as that described in Reference Example 1, the following compounds of Examples 44 and 45 were synthesized.

50 Example 44

[0109] 4-Amidino-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] propyl] aminomethylbenzene (compound No. 82 of Table 1) hydrochloride  
NMR (DMSO-d<sup>6</sup>)  
55 9.29 (br, 2H), 8.93 (br, 2H), 8.51 (t, 1H), 7.75 (d, 2H), 7.49 (d, 2H), 4.37 (m, 3H), 3.96 (d, 1H), 3.70 (m, 1H), 3.60-3.40 (m, 2H) 2.20-1.0 (m, 14H)



IR: 3227, 2922, 1657, 1607, 1539, 1485, 1458, 1323, 1246, 1032

#### Example 45

**[0110]** 4-Amidino-[(S)-N-[(R)-N'-ethoxycarbonylphenylalanyl]prolyl]aminomethylbenzene (compound No. 972 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

9.40 (br, 2H), 9.24 (br, 2H), 8.14 (t, 1H), 7.80 (d, 2H), 7.59 (t, 1H), 7.45 (d, 2H), 7.31-7.15 (m, 5H), 4.50-4.26 (m, 4H), 3.90-3.57 (m, 3H), 3.0-2.7 (m, 3H), 1.9-1.6 (m, 4H), 1.10-1.0 (m, 3H)

IR: 3279, 2364, 1637, 1539, 1491, 1450, 1255, 704

**[0111]** According to the same procedures as that described in Example 5 the following compounds of Examples 46 to 53 were synthesized.

#### Example 46

**[0112]** Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyloxy-seryl]prolyl]aminomethylcyclohexane (compound No. 240 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.88 (br, 2H), 8.71 (br, 2H), 7.72 (m, 1H), 6.39 (m, 1H), 4.59 (m, 1H), 4.52 (m, 1H), 4.11 (m, 2H), 3.86-3.71 (m, 2H), 3.58 (m, 2H), 3.22 (m, 2H), 2.79-0.88 (m, 15H), 1.24 (t, 3H), 1.15 (s, 9H)

IR: 3271, 2976, 1685, 1647, 1541, 1448, 1257, 1192, 1095, 1055

#### Example 47

**[0113]** Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl]prolyl]aminomethylcyclohexane (compound No. 977 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.74 (br, 4H), 7.68 (m, 1H), 6.01 (m, 1H), 4.83 (m, 1H), 4.57 (m, 2H), 3.74 (m, 2H), 3.50 (m, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.5-0.9 (m, 16H), 1.24 (dd, 6H), 1.09 (s, 6H), 0.81 (t, 3H)

IR: 3314, 2978, 1693, 1641, 1543, 1450, 1375, 1261, 1111, 1059

#### Example 48

**[0114]** Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl]prolyl]aminomethylcyclohexane (compound No. 978 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.75 (br, 4H), 7.55 (m, 1H), 6.40 (m, 1H), 4.52 (m, 2H), 4.13 (m, 2H), 3.88-3.70 (m, 2H), 3.55 (m, 2H), 3.28 (m, 1H), 2.87-2.70 (m, 1H), 2.20-1.20 (m, 14H), 1.27 (t, 3H), 1.09 (s, 6H), 0.81 (t, 3H), 1.10-0.90 (m, 2H)

IR: 3292, 2974, 1689, 1645, 1543, 1448, 1259, 1095, 1055

#### Example 49

**[0115]** Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-ethyl-1'-methyl-propyl)-seryl]prolyl]aminomethylcyclohexane (compound No. 979 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.78 (s, 2H), 8.69 (s, 2H), 7.55 (br, 1H), 5.99 (br, 1H), 4.84 (m, 1H), 4.54 (m, 2H), 3.71 (m, 2H), 3.49 (m, 2H), 3.20-0.90 (m, 16H), 1.64 (q, 4H), 1.23 (t, 6H), 1.03 (s, 3H), 0.78 (t, 6H)

IR: 3315, 2976, 2934, 1685, 1641, 1543, 1450, 1375, 1261, 1111

#### Example 50

**[0116]** Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-S-t-butyl-cystinyl]prolyl]aminomethylcyclohexane (compound No. 980 of Table 1) hydrochloride

NMR (DMSO-d<sup>6</sup>)

8.82 (br, 2H), 8.74 (br, 2H), 7.47 (m, 1H), 6.63 (m, 1H), 4.60-4.40 (m, 2H), 4.20-4.21 (m, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.24 (m, 1H), 2.87 (m, 2H), 2.65 (m, 1H), 2.18-1.31 (m, 12H), 1.31 (s, 9H), 1.27 (t, 3H), 1.10-0.90 (m, 2H)

IR: 3298, 2932, 1693, 1641, 1541, 1448, 1304, 1257, 1161, 1047

## Example 51

[0117] Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-methylcyclopentyl)-seryl] prolyl]aminomethylcyclohexane (compound No. 981 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.79 (br, 4H), 7.64 (m, 1H), 5.97 (m, 1H), 4.83 (m, 1H), 4.55 (m, 2H), 3.76 (m, 2H), 3.52 (m, 2H), 3.15-1.20 (m, 22H), 1.27-1.13 (m, 9H), 1.13-0.95 (m, 2H)

IR: 3329, 2934, 1684, 1639, 1541, 1450, 1261, 1182, 1111, 1060, 918

## Example 52

[0118] Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butyl-threonyl] prolyl]aminomethylcyclohexane (compound No. 982 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.74 (m, 4H), 7.80 (m, 1H), 5.66 (m, 1H), 4.85 (m, 1H), 4.57 (m, 1H), 4.29 (m, 1H), 3.80-3.60 (m, 3H), 3.05 (m, 2H), 2.60 (m, 1H), 2.50-1.20 (m, 1H), 1.27-1.22 (m, 15H), 1.15 (d, 3H), 1.10-0.90 (m, 2H)

IR: 3331, 2978, 1697, 1639, 1543, 1450, 1375, 1265, 1182, 1111

## Example 53

[0119] Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-isopropylthio-3-methyl-butanoyl] prolyl]aminomethylcyclohexane (compound No. 983 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

9.13 (br, 2H), 8.46 (br, 2H), 7.30 (m, 1H), 5.85 (m, 1H), 4.55 (m, 1H), 4.36 (m, 1H), 4.15-3.85 (m, 3H), 3.69 (m, 1H), 3.02 (m, 2H), 2.30 (m, 1H), 2.00-1.20 (m, 13H), 1.48 (s, 3H), 1.33 (s, 3H), 1.30-1.20 (m, 9H), 1.05-0.85 (m, 2H)

IR: 3420, 2974, 1635, 1556, 1521, 1448, 1385, 1298, 1259, 1060

[0120] According to the same procedures as that described in Example 11, the following compounds of Examples 54 to 80 were synthesized.

## Example 54

[0121] 4-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 391 of Table 1)

NMR (DMSO-d<sub>6</sub>)

9.55 (br, 1H), 8.31 (t, 1H), 7.59 (d, 2H), 7.24 (d, 2H), 5.73 (br, 2H), 4.57 (m, 1H), 4.26-4.32 (m, 3H), 3.91 (br, 1H), 3.40-3.60 (m, 2H), 2.05-0.80 (m, 15H)

IR: 3375, 2926, 2853, 1638, 1561, 1451, 1385, 1244

## Example 55

[0122] 4-[(S)-N-[(R)-N'-isopropoxycarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 395 of Table 1)

NMR (CDCl<sub>3</sub>)

7.65 (br, 1H), 7.53 (d, 2H), 7.29-7.19 (m, 8H), 5.89 (d, 2H), 5.01 (br, 2H), 4.58-4.45 (m, 4H), 4.27 (dd, 1H), 3.65 (br, 1H), 3.10-2.93 (m, 2H), 2.58 (q, 1H), 2.17 (br, 1H), 1.90-1.50 (m, 2H), 1.11 (d, 4H), 0.96 (d, 2H)

IR: 3331, 2980, 2880, 2365, 1639, 1539, 1452, 126

## Example 56

[0123] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-phenylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 403 of Table 1)

NMR (CDCl<sub>3</sub>)

7.80 (br, 1H), 7.47 (d, 2H), 7.40-7.14 (m, 8H), 6.11 (dd, 1H), 5.43 (dd, 1H), 4.98 (br, 2H), 4.70-4.54 (m, 2H), 4.50-4.20 (m, 1H), 4.15-4.00 (m, 1H), 4.00-3.80 (m, 2H), 3.25-3.19 (m, 1H), 2.30-1.80 (m, 4H), 1.16 (dt, 3H)

IR: 3339, 2980, 2365, 1641, 1524, 1437, 1385, 1057

## Example 57

[0124] 4-[(S)-N-[(R)-N'-ethoxycarbonyl-valyl]prolyl] aminomethylbenzamidoxime (compound No. 407 of Table 1)

NMR (CDCl<sub>3</sub>)

7.57 (br, 1H), 7.54 (d, 2H), 7.20 (d, 2H), 5.98 (d, 1H), 4.97 (br, 2H), 4.68-4.59 (m, 2H), 4.24 (dd, 1H), 4.07 (t, 1H), 4.10-4.00 (m, 1H), 3.90-3.80 (m, 1H), 3.60-3.45 (m, 2H), 2.31 (br, 1H), 2.20-1.95 (m, 4H), 1.88 (d, 1H), 1.01 (t, 3H), 0.97 (d, 6H)

IR: 3337, 2971, 2878, 2363, 1640, 1539, 1445, 1277, 1238

Example 58

[0125] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-3,3-dimethylbutanoyl] propyl] aminomethylbenzamidoxime (compound No. 409 of Table 1)

NMR (DMSO-d<sub>6</sub>)

8.01 (br, 1H), 7.59 (d, 2H), 7.21 (d, 2H), 7.19-7.15 (m, 1H), 5.73 (br, 2H), 4.36-4.24 (m, 4H), 4.0-3.60 (m, 4H), 2.10-1.80 (m, 5H), 1.06 (t, 3H), 0.96 (s, 9H)

IR: 3345, 2966, 2364, 1647, 1535, 1443, 1240

Example 59

[0126] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-heptanoyl] propyl] aminomethylbenzamidoxime (compound No. 411 of Table 1)

NMR (CDCl<sub>3</sub>)

7.63 (m, 1H), 7.51 (d, 2H), 7.20 (d, 2H), 5.85 (d, 2H), 4.99 (br, 1H), 4.67-4.58 (m, 2H), 4.35-4.28 (m, 2H), 3.99 (br, 1H), 3.86-3.80 (m, 1H), 3.58-3.50 (m, 2H), 2.31 (br, 1H), 2.07-1.90 (m, 3H), 1.80-1.50 (m, 2H), 1.40-1.10 (m, 5H), 1.03 (t, 3H), 1.01-0.84 (m, 3H)

IR: 3347, 2961, 2363, 2342, 1641, 1541, 1447, 1263, 1049

Example 60

[0127] 4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-heptanoyl] propyl] aminomethylbenzamidoxime (compound No. 412 of Table 1)

NMR (CDCl<sub>3</sub>)

7.74-7.70 (m, 1H), 7.49 (d, 2H), 7.27 (t, 1H), 7.20 (d, 2H), 5.43 (d, 1H), 4.93 (br, 2H), 4.65 (d, 1H), 4.48-4.25 (m, 3H), 3.93 (br, 1H), 3.50 (q, 1H), 2.40-2.30 (m, 1H), 2.10-1.90 (m, 3H), 1.70-1.50 (m, 2H), 1.42-1.21 (m, 13H), 0.92-0.80 (m, 3H)

IR: 3337, 2961, 2934, 2363, 1641, 1535, 1449, 1368, 1165

Example 61

[0128] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] propyl] aminomethylbenzamidoxime (compound No. 418 of Table 1)

NMR (CDCl<sub>3</sub>)

7.58-7.51 (m, 1H), 7.53 (d, 2H), 7.20 (d, 2H), 5.87 (d, 1H), 5.01 (br, 2H), 4.64-4.56 (m, 2H), 4.40 (q, 1H), 4.26 (dd, 1H), 4.10-4.00 (m, 1H), 3.84-3.78 (m, 1H), 3.53-3.47 (m, 2H), 2.32 (br, 1H), 2.10-1.90 (m, 3H), 1.61 (d, 2H), 1.00 (t, 3H), 0.97 (s, 9H)

IR: 3324, 2957, 2263, 2342, 1642, 1541, 1445, 1248, 1059

Example 62

[0129] 4-[(S)-N-[(R)-N'-(ethoxycarbonylmethyl)oxycarbonyl-phenylalanyl] propyl] aminomethylbenzamidoxime (compound No. 984 of Table 1)

NMR (CDCl<sub>3</sub>)

7.54 (d, 2H), 7.41 (br, 1H), 7.28-7.20 (m, 8H), 6.70 (d, 1H), 5.09 (br, 2H), 4.66 (dd, 1H), 4.60-4.55 (m, 2H), 4.22-4.00 (m, 4H), 4.03 (q, 2H), 3.62 (br, 1H), 3.10-3.02 (m, 2H), 2.60-2.40 (m, 1H), 2.14 (br, 1H), 2.00-1.50 (m, 3H), 1.22 (t, 3H)

IR: 3356, 3063, 2980, 2364, 1717, 1641, 1539, 1451, 1213, 702

Example 63

[0130] 4-[(S)-N-[(R)-2-ethoxycarbonylamino-cyclohexylacetyl] propyl] aminomethylbenzamidoxime (compound No.

985 of Table 1)

NMR (CDCl<sub>3</sub>)

7.52 (d, 2H), 7.54-7.50 (m, 1H), 7.20 (d, 2H), 6.03 (br, 1H), 4.97 (br, 2H), 4.68 (q, 2H), 4.22 (dd, 1H), 4.12-4.03 (m, 2H), 3.64-3.47 (m, 1H), 3.20 (s, 3H), 2.32 (br, 1H), 2.05-1.60 (m, 9H), 1.28-0.97 (m, 6H)

IR: 3343, 2928, 2853, 2365, 1639, 1541, 1449, 1260

Example 64

**[0131]** 4-[(S)-N-[(R)-2-ethoxycarbonylamino-2'-thienylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 986 of Table 1)

NMR (CDCl<sub>3</sub>)

7.80-7.60 (m, 1H), 7.46 (dd, 2H), 7.40-6.95 (m, 5H), 6.13 (dd, 1H), 5.71 (dd, 1H), 4.99 (br, 2H), 4.75-4.20 (m, 3H), 4.00-3.80 (m, 2H), 3.70-3.50 (m, 1H), 3.40-3.30 (m, 1H), 2.40-1.80 (m, 4H), 1.16 (dt, 3H)

IR: 3337, 2978, 2364, 1641, 1524, 1443, 1240, 1057, 710

Example 65

**[0132]** 4-[(S)-N-[(R)-2-ethoxycarbonylamino-4'-fluorophenylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 987 of Table 1)

NMR (CDCl<sub>3</sub>)

7.80 (t, 1H), 7.46-7.27 (m, 4H), 7.19-6.92 (m, 4H), 6.19-6.15 (m, 1H), 5.50 (dd, 1H), 5.02 (br, 2H), 4.70-4.20 (m, 3H), 4.10-3.70 (m, 4H), 3.22-3.15 (m, 1H), 2.25-1.80 (m, 4H), 1.16 (dt, 3H)

IR: 3345, 3073, 2980, 2363, 2344, 1641, 1510, 1143

Example 66

**[0133]** 4-[(S)-N-[(R)-N'-benzyloxycarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 988 of Table 1)

NMR (CDCl<sub>3</sub>)

7.50 (d, 2H), 7.49-7.30 (m, 1H), 7.26-7.12 (m, 12H), 6.40-6.10 (m, 1H), 4.85 (br, 2H), 4.90-4.70 (m, 1H), 4.55-4.40 (m, 4H), 4.30-4.20 (m, 1H), 3.70-3.60 (m, 1H), 3.03-2.95 (m, 1H), 2.20-2.15 (m, 1H), 2.00-1.45 (m, 3H)

Example 67

**[0134]** 4-[(S)-N-(R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylbenzamidoxime (compound No. 989 of Table 1)

NMR (CDCl<sub>3</sub>)

7.67 (t, 1H), 7.53 (d, 2H), 7.22 (d, 2H), 5.34 (d, 1H), 4.91 (br, 2H), 4.65 (d, 1H), 4.42-4.34 (m, 3H), 4.00-3.90 (m, 1H), 3.48 (q, 1H), 2.40-2.30 (m, 1H), 2.02-1.95 (m, 3H), 1.56-1.53 (m, 2H), 1.31 (s, 9H), 0.98 (s, 9H)

IR: 3345, 2959, 2367, 1641, 1535, 1446, 1367, 1167

Example 68

**[0135]** 4-[(S)-N-[(R)-N'-dimethylcarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 990 of Table 1)

NMR (DMSO-d<sub>6</sub>)

9.56 (s, 1H), 8.11 (t, 1H), 7.56 (d, 2H), 7.18 (d, 2H), 7.29-7.16 (m, 5H), 6.70 (d, 1H), 5.74 (br, 2H), 4.40-4.05 (m, 4H), 2.94 (d, 2H), 2.93-2.70 (m, 2H), 2.60 (s, 6H), 1.90-1.60 (m, 4H)

IR: 3306, 2932, 2880, 2363, 2341, 1634, 1541, 1453

Example 69

**[0136]** 4-[(S)-N-[(S)-N'-benzyloxycarbonyl-β-t-butylaspartyl] prolyl] aminomethylbenzamidoxime (compound No. 991 of Table 1)

NMR (CDCl<sub>3</sub>)

7.63 (br, 1H), 7.51 (d, 2H), 7.33-7.26 (m, 5H), 7.18 (d, 2H), 6.07 (d, 1H), 5.08 (dd, 2H), 4.92 (br, 2H), 4.90-4.70 (m, 1H), 4.66 (d, 1H), 4.40 (d, 2H), 3.90-3.80 (m, 2H), 3.0-2.90 (m, 1H), 2.55 (dd, 1H), 2.35-2.20 (m, 1H), 2.08-1.90 (m, 3H), 1.25 (s, 9H)

IR: 3364, 3063, 2978, 2363, 2343, 2343, 1717, 1641, 1539, 1450, 1369, 1253 1157

Example 70

5 **[0137]** Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butoxy-seryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 485 of Table 1)

NMR (CDCl<sub>3</sub>)

7.16 (m, 1H), 5.53 (m, 1H), 4.60-4.53 (m, 2H), 4.47 (s, 2H), 4.13-4.06 (m, 2H), 3.76 (br, 2H), 3.60-3.50 (m, 2H), 3.07 (br, 2H), 2.41 (m, 2H), 2.04-1.20 (m, 12H), 1.27 (t, 3H), 1.16 (s, 9H), 1.03-0.94 (m, 2H)

10 IR: 3352, 2930, 1701, 1651, 1541, 1448, 1259, 1053, 754

Example 71

15 **[0138]** Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butylseryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 486 of Table 1)

NMR (CDCl<sub>3</sub>)

7.19 (m, 1H), 5.40 (d, 1H), 4.87 (m, 1H), 4.61-4.53 (m, 2H), 4.47 (br, 2H), 3.75 (m, 2H), 3.60-3.40 (m, 2H), 3.08 (t, 2H), 2.40 (m, 1H), 2.20-1.20 (m, 12H), 1.21 (dd, 6H), 1.19 (s, 9H), 1.10-0.90 (m, 2H)

20 IR: 3356, 2976, 1697, 1649, 1541, 1448, 1261, 1190, 1109, 1022

Example 72

25 **[0139]** Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-(1',1'-dimethylpropyl)-seryl]prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 487 of Table 1)

NMR (CDCl<sub>3</sub>)

7.14 (m, 1H), 5.51 (d, 1H), 4.60-4.50 (m, 2H), 4.48 (br, 2H), 4.09 (m, 2H), 3.78 (m, 2H), 3.55-3.45 (m, 2H), 3.06 (m, 2H), 2.35 (m, 1H), 2.20-0.90 (m, 16H), 1.24 (t, 3H), 1.10 (s, 6H), 0.82 (t, 3H)

IR: 3346, 2976, 2930, 1649, 1543, 1448, 1261, 1176, 1095, 1055

30 Example 73

**[0140]** Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 488 of Table 1)

NMR (CDCl<sub>3</sub>)

35 7.18 (m, 1H), 5.38 (d, 1H), 4.86 (m, 1H), 4.61-4.50 (m, 2H), 4.47 (br, 2H), 3.77 (m, 2H), 3.57-3.42 (m, 2H), 3.06 (t, 2H), 2.39 (m, 1H), 2.20-0.90 (m, 16H), 1.23 (dd, 6H), 1.10 (s, 6H), 0.82 (t, 3H)

IR: 3346, 2976, 1703, 1651, 1541, 1448, 1263, 1178, 1109, 1030

Example 74

40 **[0141]** Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-ethyl-1'-methyl-propyl)-seryl] prolyl]aminomethylcyclohexanecarboxamidoxime (compound No. 490 of Table 1)

NMR (CDCl<sub>3</sub>)

45 7.17 (br, 1H), 5.35 (br, 1H), 4.86 (m, 1H), 4.60-4.50 (m, 2H), 4.47 (br, 2H), 3.78 (m, 2H), 3.53-3.38 (m, 2H), 3.07 (t, 2H), 2.37-1.20 (m, 17H), 1.23 (t, 6H), 1.06 (s, 3H), 1.06-0.82 (m, 2H), 0.79 (t, 6H)

IR: 3350, 2976, 2932, 1651, 1541, 1450, 1375, 1263, 1109, 1026

Example 75

50 **[0142]** Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-S-t-butyl-cystinyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 492 of Table 1)

NMR (CDCl<sub>3</sub>)

55 7.27 (m, 1H), 5.81 (m, 1H), 4.60-4.40 (m, 2H), 4.88 (br, 2H), 4.11 (m, 2H), 3.87 (m, 1H), 3.68 (m, 1H), 3.06 (m, 2H), 2.90-2.70 (m, 2H), 2.37 (m, 1H), 2.10-1.20 (m, 12H), 1.32 (s, 9H), 1.25 (t, 3H), 1.10-0.90 (m, 2H)

IR: 3346, 2930, 1699, 1649, 1541, 1448, 1257, 1163, 1051, 929

## Example 76

[0143] Trans-4-[(S)-N-[(R)-2-ethoxycarbonylamino-3-isopropylthio-3-methylbutanoyl] propyl]aminomethylcyclohexanecarboxamidoxime (compound No. 497 of Table 1)

NMR (CDCl<sub>3</sub>)

7.16 (m, 1H), 5.62 (m, 1H), 4.61 (d, 1H), 4.47 (br, 2H), 4.35 (d, 1H), 4.12 (m, 2H), 3.96 (m, 1H), 3.76 (m, 1H), 3.10 (m, 1H), 3.00 (m, 2H), 2.38 (m, 1H), 2.00-1.20 (m, 12H), 1.47 (s, 3H), 1.40 (s, 3H), 1.33-1.25 (m, 9H), 1.00-0.90 (m, 2H)

IR: 3354, 2928, 1653, 1541, 1446, 1367, 1302, 1251, 1155, 1055

## Example 77

[0144] Trans-4-[(S)-N-[(S)-N'-t-butyloxycarbonyl-seryl] propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 992 of Table 1)

NMR (CDCl<sub>3</sub>)

7.76 (br, 1H), 6.10 (br, 1H), 5.40 (br, 1H), 4.60 (br, 4H), 3.96 (br, 4H), 3.16-1.21 (m, 15H), 1.40 (s, 9H), 0.99 (br, 2H)

IR: 3314, 2978, 1691, 1639, 1541, 1450, 1367, 1165, 1049

## Example 78

[0145] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butyl-threonyl] propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 993 of Table 1)

NMR (CDCl<sub>3</sub>)

7.24 (m, 1H), 5.43 (d, 1H), 4.85 (m, 1H), 4.57 (d, 1H), 4.47 (br, 2H), 4.23 (t, 1H), 3.92 (t, 1H), 3.80-3.70 (m, 2H), 3.06 (m, 2H), 2.36 (m, 1H), 2.00-1.20 (m, 12H), 1.23 (s, 9H), 1.23 (dd, 6H), 1.15 (d, 3H), 1.10-0.90 (m, 2H)

IR: 3354, 2978, 1699, 1649, 1543, 1448, 1373, 1257, 1192, 1111, 1032

## Example 79

[0146] Trans-4-[(S)-N-[(R)-2-acetoxy-cyclohexylacetyl] propyl] aminomethylcyclohexanecarboxamidoxime (compound No. 994 of Table 1)

NMR (CDCl<sub>3</sub>)

6.80 (br, 1H), 4.61 (t, 2H), 4.49 (br, 2H), 3.90-3.84 (m, 1H), 3.51-3.40 (m, 1H), 3.10-2.85 (m, 2H), 2.38 (br, 1H), 2.11 (s, 3H), 2.06-0.80 (m, 25H)

IR: 3484, 3389, 2928, 2855, 1725, 1649, 1451, 1250

## Example 80

[0147] Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-methylcyclopentyl)-seryl] propyl]aminomethylcyclohexanecarboxamidoxime (compound No. 995 of Table 1)

NMR (CDCl<sub>3</sub>)

7.18 (m, 1H), 5.42 (m, 1H), 4.85 (m, 2H), 4.60-4.49 (m, 4H), 3.73 (m, 2H), 3.57-3.42 (m, 2H), 3.08 (m, 1H), 2.40 (m, 1H), 2.04-1.20 (m, 21H), 1.27-1.20 (m, 9H), 1.03-0.94 (m, 2H)

IR: 3356, 2932, 1695, 1653, 1541, 1448, 1263, 1111, 1030, 918

[0148] According to the same procedures as that described in Reference Example 2, the following compound of Example 81 was synthesized.

## Example 81

[0149] Trans-4-amino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyloxy-seryl] propyl] aminomethylcyclohexane (compound No. 1003 of Table 1) hydrochloride

NMR (DMSO-d<sub>6</sub>)

8.29 (s, 3H), 7.20 (s, 1H), 5.69 (d, 1H), 4.58-4.47 (m, 2H), 4.12 (m, 2H), 3.82 (m, 1H), 3.61-3.48 (m, 2H), 3.09 (m, 2H), 2.32-0.86 (m, 15H), 1.27 (t, 3H), 1.16 (s, 9H)

IR: 3358, 2974, 1645, 1541, 1448, 1257, 1192, 1053

[0150] According to the same procedures as that described in Example 67, the following compounds 126 to 130 were synthesized.

## Experimental Example 1: Determination of antithrombin activity

## (i) The measuring method for hydrolysis inhibition of synthetic substrate (S-2238)

[0151] S-2238 (manufactured by Kabi Co.) is dissolved in a Tris hydrochloric acid buffer solution (pH: 8.3) to prepare a S-2238-0.4 M Tris hydrochloric acid solution having a concentration of 80  $\mu\text{M}$ . To 175  $\mu\text{l}$  of the solution, an aqueous solution of a compound of the present invention (515  $\mu\text{l}$ ) is added. After incubating at 37°C for one minute, 10  $\mu\text{l}$  of a bovine thrombin solution (4.4 units/ml, manufactured by Mochida Co., Ltd.) is added. A hydrolysis reaction rate of the substrate is determined by measuring a change in absorbance of 405 nm at 37°C.

[0152] The inhibitor concentration exhibiting an absorbance which is half as large as that obtained in case of adding no inhibitor (compound of the present invention) was determined as  $\text{IC}_{50}$  ( $\mu\text{M}$ ).

## (ii) The measuring method for coagulation inhibition of rat plasma

[0153] The compound of the present invention is dissolved in water or saline to form a solution of a total volume of 0.1 ml. To the solution, 0.1 ml of rat plasma is added and the mixture is incubated at 37°C for 30 seconds. Then, 0.1 ml of bovine thrombin (8 units/ml, Mochida Co., Ltd.) is added and the coagulation time is measured at 37°C. The concentration of the inhibitor (i.e., the compound of the present invention) which doubles the coagulation time that obtained in the absence of the inhibitor was determined as  $\text{IC}_{50}$  ( $\mu\text{M}$ ).

## (iii) The measuring method for antithrombin activity of rat plasma on oral administration

[0154] To a rat abstained from bait overnight, an aqueous solution or suspension of the present compound (inhibitor) (30 mg/kg) is orally administered using an oral sound.

[0155] After one hour, 2 ml of blood is collected from cava abdominalis and the antithrombin activity in plasma is measured using a method of the above item (ii). As a control experiment, the coagulation time of blood collected from a rat which has not been administered the inhibitor was measured. The extension effect on the coagulation time is represented by the numerical value obtained by comparing the data with those obtained in control experiment, wherein the numerical value obtained in the control experiment was assumed to be 1.

## Experimental Example 2: Determination of Antitrypsin activity

## (i) The measuring method for hydrolysis inhibition of synthetic substrate (S-2222)

[0156] S-2222 (manufactured by Kabi Co.) is dissolved in a Tris hydrochloric acid (pH: 8.3) to prepare a S-2222-0.4M Tris hydrochloric acid solution having a concentration of 400  $\mu\text{M}$ . To the solution (175  $\mu\text{l}$ ), 515  $\mu\text{l}$  of a solution of a compound of the present invention is added. After incubating at 37°C for one minute, 10  $\mu\text{l}$  of a bovine trypsin solution (1 to 2 mg/ml, manufactured by Sigma Co.) is added. A hydrolysis reaction rate of the substrate is determined by measuring a change in absorbance of 405 nm at 37°C.

[0157] The inhibitor concentration exhibiting an absorbance which is half as large as that obtained in case of adding no inhibitor (compound of the present invention) was determined as  $\text{IC}_{50}$  ( $\mu\text{M}$ ).

[0158] The results are shown in Table 2.

Table 2

Example No.	Antithrombin activity $\text{IC}_{50}$ ( $\mu\text{M}$ )		Antitrypsin activity $\text{IC}_{50}$ ( $\mu\text{M}$ )	Thrombin coagulation time extension coagulation on oral administration
	Synthetic substrate method	Rat plasma method		
Ref 1				
1		0.056		3.16
3	0.72	0.59		
5	0.011	0.038	2.2	
6	0.021		1.7	

Table 2 (continued)

Example No.	Antithrombin activity IC <sub>50</sub> (μm)		Antitrypsin activity IC <sub>50</sub> (μm)	Thrombin coagulation time extension coagulation on oral administration
	Synthetic substrate method	Rat plasma method		
Ref 1				
7	0.015	0.053	3.2	
8	0.021		1.0	
9	0.014		0.94	
10	0.017	0.058	3.6	
11				3.28
12		> 300		2.82
13				4.16
14				3.52
15				4.35
16				2.75
17				2.77
18				3.58
19				3.99
20				3.72
21				2.85
22				4.37
23				2.37
24				2.70
25				2.94
26				4.36
27				3.09
28				2.16
29				2.34
30				
31				
32				
33				
34				
Ref 2				
	0.13	0.045	14	4.10
36	0.13	0.080	14	2.10
37		0.082		
38		0.097		2.35
41		0.056		
42		0.088		2.18
43		0.13		1.25

## Experimental Example 3: Acute toxicity test

[0159] Acute toxicity was determined in rat. An approximate lethal dose was determined by conducting an oral acute toxicity test using rats. The results are shown in Table 3.

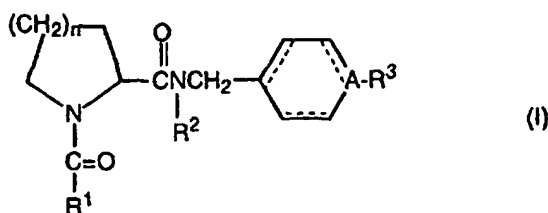


Table 3

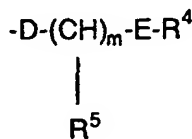
	Approximate lethal dose mg/kg	
	Male	Female
Example No.		
Ref 2	Not less than 2000	Not less than 2000
20	Not less than 2000	Not less than 2000
24	Not less than 2000	Not less than 2000

## Claims

1. A prolineamide derivative represented by the formula (I):



wherein A is a carbon atom or a nitrogen atom;  
 n is an integer of 0 to 2;  
 a broken line is no bond or a single bond;  
 R¹ is



[wherein D and E independently indicate a single bond or an optionally branched C₁-C₆ alkylene group;

R⁴ is a C₁-C₆ alkyl group; -OR⁶ (R⁶ is a hydrogen atom, a C₁-C₆ alkyl group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group or an optionally substituted C₇-C₁₂ aralkyl group), -SR⁷ (R⁷ is a C₁-C₆ alkyl group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group or an optionally substituted C₇-C₁₂ aralkyl group), -SOR⁸ (R⁸ is an optionally substituted C₆-C₁₀ aryl group or an optionally substituted C₃-C₈ cycloalkyl group), -SO₂R⁹ (R⁹ is an optionally substituted C₆-C₁₀ aryl group or an optionally substituted C₃-C₈ cycloalkyl group), -COR¹⁰ (R¹⁰ is a hydroxyl group, a C₁-C₆ alkoxy group, an optionally substituted C₆-C₁₀ aryl group or an optionally substituted C₃-C₈ cycloalkyl group), -NHR¹¹ (R¹¹ is a C₁-C₆ alkyl group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group or an optionally substituted C₇-C₁₂ aralkyl group), -NHCOR¹² (R¹² is a C₁-C₆ alkoxy group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group or an optionally substituted C₇-C₁₂ aralkyloxy group), -NHSO₂R¹³ (R¹³ is a C₁-C₆ alkyl group, an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group, an optionally substituted C₇-C₁₂ aralkyl group, or an optionally substituted 5- to 10-membered heterocyclic group), an optionally substituted C₆-C₁₀ aryl group, an optionally substituted C₃-C₈ cycloalkyl group, an optionally substituted 5- to 10-membered heterocyclic group or -SiR¹⁴R¹⁵R¹⁶ (R¹⁴, R¹⁵, and R¹⁶ independently indicate a C₁-C₆ alkyl group);

R⁵ is a -OR¹⁷ (R¹⁷ is a hydrogen atom, -SiR²²R²³R²⁴ (R²², R²³, and R²⁴ independently indicate a C₁-C₆ alkyl group), a C₁-C₆ alkyl group, or an optionally substituted 5- to 10-membered heterocyclic group), -OCOR¹⁸ (R¹⁸

is a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, an amino group, a C<sub>1</sub>-C<sub>6</sub> alkylamino group, a C<sub>2</sub>-C<sub>12</sub> dialkylamino group or a C<sub>2</sub>-C<sub>7</sub> alkenylamino group), -NHR<sup>19</sup> (R<sup>19</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group), -NHCOR<sup>20</sup> (R<sup>20</sup> is a hydrogen atom, a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> haloalkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, an optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkenyloxy group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group, a C<sub>2</sub>-C<sub>12</sub> dialkylamino group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> haloalkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, an optionally substituted C<sub>6</sub>-C<sub>10</sub> aryl group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkyl group or an optionally substituted C<sub>7</sub>-C<sub>12</sub> aralkyl group); and m is 0 or 1;

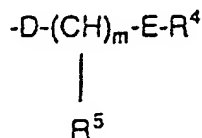
each of said 5- to 10-membered heterocyclic groups is independently selected from a furan ring, a tetrahydrofuran ring, a pyran ring, a benzofuran ring, a chroman ring, a thiophene ring, a benzothiophene ring, a pyrrole ring, an imidazole ring, a pyrazole ring, a triazole ring, a pyridine ring, a piperidine ring, a pyrazine ring, a piperazine ring, a pyrimidine ring, an indole ring, a benzimidazole ring, a purine ring, a quinoline ring, a phthalazine ring, a quinazoline ring, a cinnoline ring, an oxazole ring, a thiazole ring and a morpholine ring;

each of said optional substituents being independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> haloalkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyloxy group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>8</sub>-C<sub>13</sub> aralkyloxycarbonyl group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarboxyalkoxy group and a halogen atom);

R<sup>2</sup> is a hydrogen atom or a C<sub>1</sub>-C<sub>6</sub> alkyl group; and R<sup>3</sup> is -C(=NR<sup>25</sup>)NH<sub>2</sub> (wherein R<sup>25</sup> is a hydrogen atom or a hydroxyl group) or -NH<sub>2</sub>; provided that R<sup>3</sup> is -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> is as defined above) when A is a nitrogen atom, or a salt or hydrate thereof;

with the proviso that if the substituent R<sup>2</sup> represents a hydrogen atom, the group "D" represents a single bond, and the index n is 1 or 2, then neither of the substituents R<sup>4</sup> or R<sup>5</sup> represents a group including an amino-sulfonyl moiety.

2. A compound according to Claim 1, wherein A is a carbon atom.
3. A compound according to Claim 1 or Claim 2, wherein n is 1 or 2; R<sup>1</sup> is

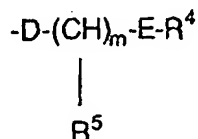


{wherein D and E independently indicate a single bond or an optionally branched C<sub>1</sub>-C<sub>6</sub> alkylene group;

R<sup>4</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; -OR<sup>6</sup> (R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C<sub>7</sub>-C<sub>12</sub> aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -SR<sup>7</sup> (R<sup>7</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C<sub>7</sub>-C<sub>12</sub> aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -COOH; a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>2</sub>-C<sub>7</sub> acyl group, a C<sub>2</sub>-C<sub>7</sub> acyloxy group, a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; a C<sub>3</sub>-C<sub>8</sub> cycloalkyl group; or -SiR<sup>14</sup>R<sup>15</sup>R<sup>16</sup> (R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> independently indicate a C<sub>1</sub>-C<sub>6</sub> alkyl group);

$R^5$  is -OH, -OCOR<sup>18</sup> ( $R^{18}$  is a C<sub>1</sub>-C<sub>6</sub> alkoxy group or a C<sub>2</sub>-C<sub>7</sub> alkenylamino group), -NH<sub>2</sub>, -NHCOR<sup>20</sup> ( $R^{20}$  is a C<sub>1</sub>-C<sub>6</sub> alkoxy group, a C<sub>6</sub>-C<sub>10</sub> aryloxy group, a C<sub>3</sub>-C<sub>9</sub> alkoxy carbonylalkoxy group, a C<sub>2</sub>-C<sub>12</sub> dialkylamino group or a C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> ( $R^{21}$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group, a C<sub>6</sub>-C<sub>10</sub> aryl group, a C<sub>3</sub>-C<sub>9</sub> alkoxy carbonylalkyl group or a C<sub>7</sub>-C<sub>12</sub> aralkyl group); and  $m$  is 0 or 1; and  $R^2$  is a hydrogen atom.

4. A compound according to Claim 1 or Claim 2, wherein  $n$  is 1;  $R^1$  is



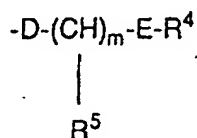
{wherein D and E independently indicate a single bond or an optionally branched C<sub>1</sub>-C<sub>6</sub> alkylene group;

$R^4$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group; -OR<sup>6</sup> ( $R^6$  is a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group or C<sub>7</sub>-C<sub>12</sub> aralkyl group); -SR<sup>7</sup> ( $R^7$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group); a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group; or a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group;

$R^5$  is -OH, NH<sub>2</sub>, -NHCOR<sup>20</sup> ( $R^{20}$  is a C<sub>1</sub>-C<sub>6</sub> alkoxy group or a C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> ( $R^{21}$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group or a C<sub>6</sub>-C<sub>10</sub> aryl group); and  $m$  is 1; and

$R^2$  is a hydrogen atom,

5. A compound according to Claim 1 or Claim 2, wherein  $n$  is 1;  $R^1$  is



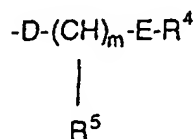
{wherein D is a single bond; E is a single bond or a C<sub>1</sub>-C<sub>6</sub> alkylene group;

$R^4$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group; -OR<sup>6</sup> ( $R^6$  is a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one substituent selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group or C<sub>7</sub>-C<sub>12</sub> aralkyl group); -SR<sup>7</sup> ( $R^7$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group); a C<sub>6</sub>-C<sub>10</sub> aryl group which may be substituted with at least one or more substituents selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a halogen atom, a carboxyl group, a C<sub>2</sub>-C<sub>7</sub> carboxyalkyl group and a benzyloxycarbonyl group; or a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group;

$R^5$  is -NH<sub>2</sub>, -NHCOR<sup>20</sup> ( $R^{20}$  is a C<sub>1</sub>-C<sub>6</sub> alkoxy group or a C<sub>7</sub>-C<sub>12</sub> aralkyloxy group) or -NHSO<sub>2</sub>R<sup>21</sup> ( $R^{21}$  is a C<sub>1</sub>-C<sub>6</sub> alkyl group or a C<sub>6</sub>-C<sub>10</sub> aryl group); and  $m$  is 1; and

$R^2$  is a hydrogen atom.

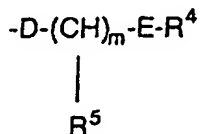
6. A compound according to claim 1, wherein A is a carbon atom;  $n$  is 1;  $R^1$  is



{wherein D is a single bond; E is a single bond or a C<sub>1</sub>-C<sub>3</sub> alkylene group;  $R^4$  is a C<sub>3</sub>-C<sub>6</sub> alkyl group; -OR<sup>6</sup> ( $R^6$  is

a C<sub>1</sub>-C<sub>6</sub> alkyl group, a phenyl group, or a C<sub>3</sub>-C<sub>6</sub> cycloalkyl group; R<sup>5</sup> is -OH, -NHR<sup>19</sup> (R<sup>19</sup> is a hydrogen atom), -NHCOR<sup>20</sup> (R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group) or -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> is a C<sub>1</sub>-C<sub>3</sub> alkyl group); and m is 1; and R<sup>2</sup> is a hydrogen atom.

7. A compound according to Claim 1 or Claim 2, wherein n is 1; R<sup>1</sup> is

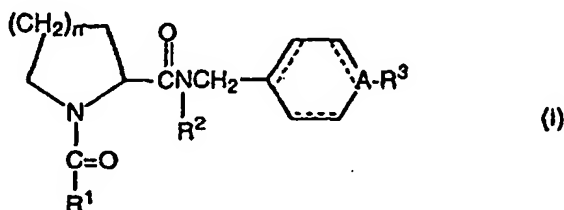


- {D is a single bond; E is a single bond or a C<sub>1</sub>-C<sub>6</sub> alkylene group; R<sup>4</sup> is a C<sub>1</sub>-C<sub>6</sub> alkyl group; R<sup>5</sup> is -NHCOR<sup>20</sup> (R<sup>20</sup> is a C<sub>1</sub>-C<sub>6</sub> alkoxy group); and m is 1}; R<sup>2</sup> is a hydrogen atom; and R<sup>3</sup> is -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> is a hydrogen atom or a hydroxyl group).

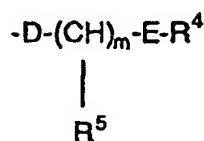
8. Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl) propyl]aminomethylcyclohexanecarboxamidoxime or a salt or hydrate thereof.
9. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 8 and a pharmaceutically acceptable carrier therefor.
10. The use of a compound as claimed in any one of claims 1 to 8 in the manufacture of a medicament effective as a protease inhibitor.
11. A compound according to any of claims 1-8 for use as a medicament.
12. Use of a compound according to any of claims 1-8 for the manufacture of an anti-coagulant medicament.
13. Use of a compound according to any of claims 1-8 for the manufacture of a medicament for the treatment of pancreatitis.

#### Patentansprüche

1. Prolinamidderivat, dargestellt durch die Formel (I):



- wobei A ein Kohlenstoffatom oder ein Stickstoffatom ist; n eine ganze Zahl von 0 bis 2 ist; eine gestrichelte Linie keine Bindung oder eine Einfachbindung ist; R<sup>1</sup>



ist (wobei D und E unabhängig voneinander eine Einfachbindung oder eine gegebenenfalls verzweigte C<sub>1</sub>-C<sub>6</sub>-Alkylengruppe bedeuten;

R<sup>4</sup> eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; -OR<sup>6</sup> (R<sup>6</sup> ist ein Wasserstoffatom, eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe), -SR<sup>7</sup> (R<sup>7</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe), -SOR<sup>8</sup> (R<sup>8</sup> ist eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe oder eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe), -SO<sub>2</sub>R<sup>9</sup> (R<sup>9</sup> ist eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe oder eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe), -COR<sup>10</sup> (R<sup>10</sup> ist eine Hydroxylgruppe, eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe oder eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe), -NHR<sup>11</sup> (R<sup>11</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe), -NHCOR<sup>12</sup> (R<sup>12</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkyloxygruppe), -NHSO<sub>2</sub>R<sup>13</sup> (R<sup>13</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe, eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe oder eine gegebenenfalls substituierte 5- bis 10-gliedrige heterozyklische Gruppe), eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe, eine gegebenenfalls substituierte 5- bis 10-gliedrige heterozyklische Gruppe oder -SiR<sup>14</sup>R<sup>15</sup>R<sup>16</sup> ist (R<sup>14</sup>, R<sup>15</sup> und R<sup>16</sup> bedeuten unabhängig voneinander eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe);

R<sup>5</sup> -OR<sup>17</sup> (R<sup>17</sup> ist ein Wasserstoffatom, -SiR<sup>22</sup>R<sup>23</sup>R<sup>24</sup> (R<sup>22</sup>, R<sup>23</sup> und R<sup>24</sup> bedeuten unabhängig voneinander eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe), eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe oder eine gegebenenfalls substituierte 5- bis 10-gliedrige heterozyklische Gruppe), -OCOR<sup>18</sup> (R<sup>18</sup> ist ein Wasserstoffatom, eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, eine Aminogruppe, eine C<sub>1</sub>-C<sub>6</sub>-Alkylaminogruppe, eine C<sub>2</sub>-C<sub>12</sub>-Dialkylaminogruppe oder eine C<sub>2</sub>-C<sub>7</sub>-Alkenylaminogruppe), -NHR<sup>19</sup> (R<sup>19</sup> ist ein Wasserstoffatom, eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe), -NHCOR<sup>20</sup> (R<sup>20</sup> ist ein Wasserstoffatom, eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine C<sub>1</sub>-C<sub>6</sub>-Halogenalkylgruppe, eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, eine gegebenenfalls substituierte C<sub>3</sub>-C<sub>8</sub>-Cycloalkylgruppe, eine C<sub>2</sub>-C<sub>7</sub>-Carboxyalkyloxygruppe, eine C<sub>2</sub>-C<sub>7</sub>-Alkenyloxygruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Aryloxygruppe, eine C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe, eine C<sub>2</sub>-C<sub>12</sub>-Dialkylaminogruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkyloxygruppe) oder -NHSO<sub>2</sub>R<sup>21</sup> ist (R<sup>21</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine C<sub>1</sub>-C<sub>6</sub>-Halogenalkylgruppe, eine C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, eine gegebenenfalls substituierte C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkylgruppe oder eine gegebenenfalls substituierte C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe); und m 0 oder 1 ist;

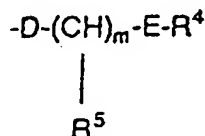
jeder der 5- bis 10-gliedrigen heterozyklischen Gruppen unabhängig voneinander ausgewählt wird aus einem Furanring, einem Tetrahydrofuranring, einem Pyranring, einem Benzofuranring, einem Chromanring, einem Thio-phenring, einem Benzothiophenring, einem Pyrrolring, einem Imidazolring, einem Pyrazolring, einem Triazolring, einem Pyridinring, einem Piperidinring, einem Pyrazinring, einem Piperazinring, einem Pyrimidinring, einem Indolring, einem Benzimidazolring, einem Purinring, einem Chinolinring, einem Phthalazinring, einem Chinazolinring, einem Cinnolinring, einem Oxazolring, einem Thiazolring und einem Morpholinring;

jeder der optionalen Substituenten unabhängig voneinander ausgewählt wird aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Halogenalkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einer Hydroxylgruppe, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonyloxygruppe, einer C<sub>8</sub>-C<sub>13</sub>-Aralkyloxy-carbonylgruppe, einer C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carboxyalkoxygruppe und einem Halogenatom);

R<sup>2</sup> ein Wasserstoffatom oder eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe ist; und R<sup>3</sup> -C(=NR<sup>25</sup>)NH<sub>2</sub> (wobei R<sup>25</sup> ein Wasserstoffatom oder eine Hydroxylgruppe ist) oder -NH<sub>2</sub> ist; vorausgesetzt, dass R<sup>3</sup> -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> ist wie oben definiert) ist, wenn A ein Stickstoffatom ist, oder ein Salz oder Hydrat davon;

mit der Maßgabe, dass falls der Substituent R<sup>2</sup> ein Wasserstoffatom darstellt, die Gruppe "D" eine Einfachbindung darstellt und der Index n 1 oder 2 ist, keiner der Substituenten R<sup>4</sup> oder R<sup>5</sup> eine Gruppe darstellt, die einen Aminosulfonylrest einschließt.

2. Verbindung gemäß Anspruch 1, wobei A ein Kohlenstoffatom ist.
3. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 oder 2 ist; R<sup>1</sup>



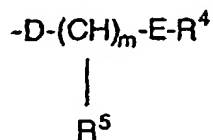
ist {wobei D und E unabhängig voneinander eine Einfachbindung oder eine gegebenenfalls verzweigte C<sub>1</sub>-C<sub>6</sub>-Alkylengruppe darstellen;

R<sup>4</sup> eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; -OR<sup>6</sup> (R<sup>6</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonyloxygruppe, einer C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe und einer Benzyloxy-carbonylgruppe besteht; oder einer C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe ist, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonyloxygruppe, einer C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe und einer Benzyloxy-carbonylgruppe besteht); -SR<sup>7</sup> (R<sup>7</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonyloxygruppe, einer C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe und einer Benzyloxy-carbonylgruppe besteht); oder eine C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonyloxygruppe, einer C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe und einer Benzyloxy-carbonylgruppe besteht); -COOH; eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einer C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Acyloxygruppe, einer C<sub>2</sub>-C<sub>7</sub>-Alkoxy-carbonyloxygruppe, einer C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe und einer Benzyloxy-carbonylgruppe besteht; eine C<sub>3</sub>-C<sub>8</sub>-Cy-cloalkylgruppe; oder -SiR<sup>14</sup>R<sup>15</sup>R<sup>16</sup> ist (R<sup>14</sup>, R<sup>15</sup> und R<sup>16</sup> bedeuten unabhängig voneinander eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe);

R<sup>5</sup> -OH, -OCOR<sup>18</sup> (R<sup>18</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe oder eine C<sub>2</sub>-C<sub>7</sub>-Alkenylaminogruppe), -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe, einer C<sub>6</sub>-C<sub>10</sub>-Aryloxygruppe, eine C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkoxygruppe, eine C<sub>2</sub>-C<sub>12</sub>-Dialkylaminogruppe oder eine C<sub>7</sub>-C<sub>12</sub>-Aralkyloxygruppe) oder -NHSO<sub>2</sub>R<sup>21</sup> ist (R<sup>21</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe, eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, eine C<sub>3</sub>-C<sub>9</sub>-Alkoxy-carbonylalkylgruppe oder eine C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe); und m 0 oder 1 ist }; und

R<sup>2</sup> ein Wasserstoffatom ist.

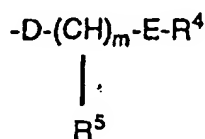
4. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 ist; R<sup>1</sup>



ist {wobei D und E unabhängig voneinander eine Einfachbindung oder eine gegebenenfalls verzweigte C<sub>1</sub>-C<sub>6</sub>-Alkylengruppe darstellen;

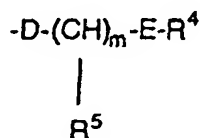
R<sup>4</sup> eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; -OR<sup>6</sup> (R<sup>6</sup> ist eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe oder C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe) besteht; -SR<sup>7</sup> (R<sup>7</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe); eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe besteht; oder eine C<sub>3</sub>-C<sub>6</sub>-Cycloalkylgruppe ist;  
 R<sup>5</sup> -OH, NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe oder eine C<sub>7</sub>-C<sub>12</sub>-Aralkyloxygruppe) oder -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe oder eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe); und m 1 ist; und  
 R<sup>2</sup> ein Wasserstoffatom ist.

5. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 ist; R<sup>1</sup>



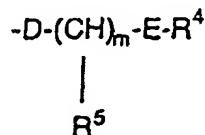
ist {wobei D eine Einfachbindung ist; E eine Einfachbindung oder eine C<sub>1</sub>-C<sub>6</sub>-Alkylengruppe ist; R<sup>4</sup> eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; -OR<sup>6</sup> (R<sup>6</sup> ist eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem Substituenten substituiert sein kann, der aus der Gruppe ausgewählt wird, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe oder einer C<sub>7</sub>-C<sub>12</sub>-Aralkylgruppe besteht); -SR<sup>7</sup> (R<sup>7</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe); eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe, die mit mindestens einem oder mehreren Substituenten substituiert sein kann, die aus der Gruppe ausgewählt werden, die aus einer C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, einem Halogenatom, einer Carboxylgruppe, einer C<sub>2</sub>-C<sub>7</sub>-Carboxyalkylgruppe und einer Benzyloxycarbonylgruppe besteht; oder eine C<sub>3</sub>-C<sub>6</sub>-Cycloalkylgruppe ist;  
 R<sup>5</sup> -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe oder eine C<sub>7</sub>-C<sub>12</sub>-Aralkyloxygruppe) oder -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe oder eine C<sub>6</sub>-C<sub>10</sub>-Arylgruppe); und m 1 ist; und  
 R<sup>2</sup> ein Wasserstoffatom ist.

6. Verbindung gemäß Anspruch 1, wobei A ein Kohlenstoffatom ist; n 1 ist; R<sup>1</sup>



ist {wobei D eine Einfachbindung ist; E eine Einfachbindung oder eine C<sub>1</sub>-C<sub>3</sub>-Alkylengruppe ist; R<sup>4</sup> eine C<sub>3</sub>-C<sub>6</sub>-Alkylgruppe, oder -OR<sup>6</sup> (R<sup>6</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe, eine Phenylgruppe oder eine C<sub>3</sub>-C<sub>6</sub>-Cycloalkylgruppe); R<sup>5</sup> -OH, -NHR<sup>19</sup> (R<sup>19</sup> ist ein Wasserstoffatom), -NHCOR<sup>20</sup> (R<sup>20</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe) oder -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> ist eine C<sub>1</sub>-C<sub>3</sub>-Alkylgruppe); und m 1 ist; und  
 R<sup>2</sup> ein Wasserstoffatom ist.

7. Verbindung gemäß Anspruch 1 oder 2, wobei n 1 ist; R<sup>1</sup>



ist {D ist eine Einfachbindung; E ist eine Einfachbindung oder eine C<sub>1</sub>-C<sub>6</sub>-Alkylengruppe; R<sup>4</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkylgruppe; R<sup>5</sup> ist -NHCOR<sup>20</sup> (R<sup>20</sup> ist eine C<sub>1</sub>-C<sub>6</sub>-Alkoxygruppe); und m 1};

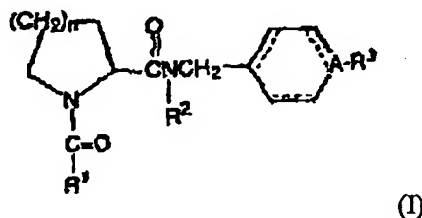
$R^2$  ein Wasserstoffatom ist; und

$R^3 - C(=NR^{25})NH_2$  ist ( $R^{25}$  ist ein Wasserstoffatom oder eine Hydroxylgruppe).

8. Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl)propyl]aminomethylcyclohexancarboxamido-  
xim oder ein Salz oder Hydrat davon.
9. Pharmazeutische Zusammensetzung umfassend eine Verbindung wie in einem der Ansprüche 1 bis 8 beansprucht und einen pharmazeutisch akzeptablen Träger dafür.
10. Verwendung einer Verbindung wie in einem der Ansprüche 1 bis 8 beansprucht zur Herstellung eines Medikaments, das als Proteaseinhibitor wirksam ist.
11. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung als Medikament.
12. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 8 zur Herstellung eines gerinnungshemmenden Medikaments.
13. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 8 zur Herstellung eines Medikaments zur Behandlung von Pankreatitis.

## Revendications

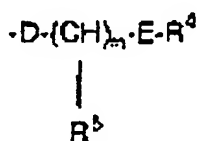
1. Dérivé de la prolinamide représenté par la formule (I):



dans laquelle A est un atome de carbone ou un atome d'azote ;

n est un entier de 0 à 2 ; une ligne pointillée représente une absence de liaison ou une simple liaison ;

$R^1$  est



{dans laquelle D et E indiquent séparément une simple liaison ou un groupe alkylène en  $C_1$  à  $C_6$  qui peut être facultativement ramifié ;

$R^4$  représente un groupe alkyle en  $C_1$  à  $C_6$ ;  $-OR^6$  ( $R^6$  est un atome d'hydrogène, un groupe alkyle en  $C_1$  à  $C_6$ , un groupe aryle en  $C_6$  à  $C_{10}$  que l'on peut facultativement substituer, un groupe cycloalkyle en  $C_3$  à  $C_8$  que l'on peut facultativement substituer ou un groupe aralkyle en  $C_7$  à  $C_{12}$  que l'on peut facultativement substituer),  $-SR^7$  ( $R^7$  représente un groupe alkyle en  $C_1$  à  $C_6$ , un groupe aryle en  $C_6$  à  $C_{10}$  que l'on peut facultativement substituer, un groupe cycloalkyle en  $C_3$  à  $C_8$  que l'on peut facultativement substituer ou un groupe aralkyle en  $C_7$  à  $C_{12}$  que l'on peut facultativement substituer),  $-SOR^8$  ( $R^8$  est un groupe aryle en  $C_6$  à  $C_{10}$  que l'on peut facultativement substituer ou un groupe cycloalkyle en  $C_3$  à  $C_8$  que l'on peut facultativement substituer),  $-SO_2R^9$  ( $R^9$  est un groupe aryle en  $C_6$  à  $C_{10}$  que l'on peut facultativement substituer ou un groupe cycloalkyle en  $C_3$  à  $C_8$  que l'on



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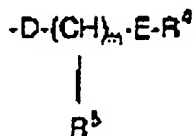
{dans laquelle D et E indiquent séparément une simple liaison ou un groupe alkylène ramifié en C<sub>1</sub> à C<sub>6</sub>;

R<sup>4</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>; -OR<sup>6</sup> (R<sup>6</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>; un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peuvent être substitués avec au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub> et d'un groupe benzyloxycarbonyle; ou un groupe aralkyle en C<sub>7</sub> à C<sub>12</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub>, et d'un groupe benzyloxycarbonyle); -SR<sup>7</sup> (R<sup>7</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>; un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub>, et d'un groupe benzyloxycarbonyle; ou un groupe aralkyle en C<sub>7</sub> à C<sub>12</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub>, et d'un groupe benzyloxycarbonyle); -COOH; un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe hydroxyle, d'un groupe carboxyle, d'un groupe alcoxycarbonyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyle en C<sub>2</sub> à C<sub>7</sub>, d'un groupe acyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonyloxy en C<sub>2</sub> à C<sub>7</sub>, d'un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub> et d'un groupe benzyloxycarbonyle; d'un groupe cycloalkyle en C<sub>3</sub> à C<sub>8</sub>; ou -SiR<sup>14</sup>R<sup>15</sup>R<sup>16</sup> (R<sup>14</sup>, R<sup>15</sup>, et R<sup>16</sup> indiquent séparément un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>);

R<sup>5</sup> est -OH, -OCOR<sup>18</sup> (R<sup>18</sup> est un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub> ou un groupe alkénylamine en C<sub>2</sub> à C<sub>7</sub>), -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> est un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>, un groupe aryloxy en C<sub>6</sub> à C<sub>10</sub>, un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub>, un groupe dialkylamine en C<sub>2</sub> à C<sub>12</sub> ou un groupe aralkyloxy en C<sub>7</sub> à C<sub>12</sub>) ou -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub>, un groupe aryle en C<sub>6</sub> à C<sub>10</sub>, un groupe alcoxycarbonylalcoyle en C<sub>3</sub> à C<sub>9</sub> ou un groupe aralkyle en C<sub>7</sub> à C<sub>12</sub>); et m a la valeur 0 ou 1; et

R<sup>2</sup> est un atome d'hydrogène.

4. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1; R<sup>1</sup> est



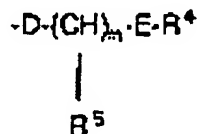
{dans laquelle D et E indiquent séparément une simple liaison ou un groupe alkylène en C<sub>1</sub> à C<sub>6</sub> éventuellement ramifié;

R<sub>4</sub> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>; -OR<sup>6</sup> (R<sup>6</sup> est un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub> et d'un groupe benzyloxycarbonyle ou d'un groupe aralkyle en C<sub>7</sub> à C<sub>12</sub>); -SR<sup>7</sup> (R<sup>7</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>); un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub> et d'un groupe benzyloxycarbonyle; ou un groupe cycloalkyle en C<sub>3</sub> à C<sub>6</sub>;

R<sup>5</sup> est représenté par -OH, NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> ou un groupe aralkyloxy en C<sub>7</sub> à C<sub>12</sub>) ou -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> ou un groupe aryle en C<sub>6</sub> à C<sub>10</sub>) et m a la valeur 1; et

R<sup>2</sup> est un atome d'hydrogène.

5. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1 ; R<sup>1</sup> est



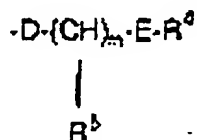
{dans laquelle D est une simple liaison ; E est une simple liaison ou un groupe alkylène en C<sub>1</sub> à C<sub>6</sub> ;

R<sub>4</sub> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> ; -OR<sup>6</sup> (R<sub>6</sub> est un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peut être substitué par au moins un substituant choisi parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub> et d'un groupe benzyloxycarbonyl ou d'un groupe aralkyle en C<sub>7</sub> à C<sub>12</sub>) ; -SR<sup>7</sup> (R<sup>7</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>) ; un groupe aryle en C<sub>6</sub> à C<sub>10</sub> qui peut être substitué par au moins un ou plusieurs substituants choisis parmi le groupe composé d'un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, d'un atome d'halogène, d'un groupe carboxyle, d'un groupe carboxyalkyle en C<sub>2</sub> à C<sub>7</sub> et d'un groupe benzyloxycarbonyl ; ou d'un groupe cycloalkyle en C<sub>3</sub> à C<sub>6</sub> ;

R<sup>5</sup> est représenté par -NH<sub>2</sub>, -NHCOR<sup>20</sup> (R<sup>20</sup> est un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub> ou un groupe aralkyloxy en C<sub>7</sub> à C<sub>12</sub>) ou -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> ou un groupe aryle en C<sub>6</sub> à C<sub>10</sub>) ; et m a la valeur 1 ; et

R<sup>2</sup> est un atome d'hydrogène.

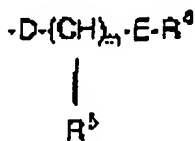
6. Composé selon la revendication 1, dans lequel A est un atome de carbone ; n a la valeur 1 ; R<sup>1</sup> est



{dans laquelle D est une simple liaison ; E est une simple liaison ou un groupe alkylène en C<sub>1</sub> à C<sub>3</sub> ; R<sup>4</sup> est un groupe alkyle en C<sub>3</sub> à C<sub>6</sub> ; -OR<sup>6</sup> (R<sup>6</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub>, un groupe phényle, ou un groupe cycloalkyle en C<sub>3</sub> à C<sub>6</sub> ; R<sup>5</sup> est représenté par -OH, -NHR<sup>19</sup> (R<sup>19</sup> est un atome d'hydrogène), -NHCOR<sup>20</sup> (R<sup>20</sup> est un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>) ou -NHSO<sub>2</sub>R<sup>21</sup> (R<sup>21</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>3</sub>) ; et m a la valeur 1 ; et

R<sup>2</sup> est un atome d'hydrogène.

7. Composé selon la revendication 1 ou la revendication 2, dans lequel n a la valeur 1 ; R<sup>1</sup> est



{D est une simple liaison ; E est une simple liaison ou un groupe alkylène en C<sub>1</sub> à C<sub>6</sub> ; R<sup>4</sup> est un groupe alkyle en C<sub>1</sub> à C<sub>6</sub> ; R<sup>5</sup> est -NHCOR<sup>20</sup> (R<sup>20</sup> est un groupe alcoyle en C<sub>1</sub> à C<sub>6</sub>) ; et m a la valeur 1 ;

R<sup>2</sup> est un atome d'hydrogène ; et

R<sup>3</sup> est représenté par -C(=NR<sup>25</sup>)NH<sub>2</sub> (R<sup>25</sup> est un atome d'hydrogène ou un groupe hydroxyle).

8. Trans-4-[(S)-N-((R)-2-éthoxycarbonylamino-4,4-diméthylpentanoyl)propyl] aminométhylcyclohexanecarboxamidoxime ou un sel ou un hydrate qui en dérivent.

9. Composition pharmaceutique comportant un composé selon l'une quelconque des revendications 1 à 8 et de ce fait un support pharmaceutiquement acceptable.

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10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament efficace comme inhibiteur de protéase.

11. Composé selon l'une quelconque des revendications 1 à 8 pour une utilisation comme médicament.

12. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament anticoagulant.

13. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament pour le traitement de la pancréatite.